Clinical trial results:
ARomatase Inhibition plus minus SaracaTinib as Advanced breast CAncer Therapy: a randomised phase II study of aromatase inhibition plus/minus the src-inhibitor AZD0530 in post-menopausal women with advanced breast cancer.

Summary

EudraCT number	2011-002157-64
Trial protocol	GB
Global end of trial date	30 April 2017

Results information

Result version number	v1 (current)
This version publication date	14 March 2020
First version publication date	14 March 2020

Trial information

Trial identification

Sponsor protocol code	v1.2 (14/04/2016)

Additional study identifiers

ISRCTN number	ISRCTN23804370
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Common Services Agency
Sponsor organisation address	CSA at NHS NSS, Gyle Square, 1 South Gyle Cresent, Edinburgh, United Kingdom, EH12 9EB
Public contact	Eve Macdonald Chisholm, Scottish Clinical Trials Research Unit National Services Scotland, +44 01312757058, eve.macdonald.chisholm@nhs.net
Scientific contact	Professor David Cameron, Cancer Research UK Edinburgh Centre, +44 0131 651 8510, David.Cameron@igmm.ed.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	20 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2017
Global end of trial reached?	Yes
Global end of trial date	30 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research objective is to see whether patients taking an aromatase inhibitor in combination with saracatinib have a longer progression free survival (surving without their cancer growing or spreading) than the patients who are taking aromatase inhibitor with placebo.

Protection of trial subjects:

No specific additional measures were implemented for this trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 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: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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)	70
From 65 to 84 years	69
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

51% patients failed screening (conmeds, out of range labs [LFTs, EGFR, blood counts], HER2 status, performance status, comorbidities, not menopausal, disease not confirmed).
27% patients refused (did not want extra tests/travel/procedures; anxious about side effects; external influences.

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, Data analyst

Blinding implementation details:

A centralised registration system will be used to assign patients to treatment groups. The packaging and tablets will appear identical for both active and matching placebo treatments. The label attached to each package of blinded study material will have a unique treatment kit number that is linked to the randomisation scheme.

Arms

Are arms mutually exclusive?	Yes
Arm title	AI plus Saracatinib

Arm description:

Patients will receive an aromatase inhibitor and saracatinib (AZD0530). Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus saracatinib 175 mg daily. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus saracatinib 175 mg daily. Saracatinib (AZD0530) is an oral Src inhibitor and can be administered with or without food.

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	
Other name	AZD0530
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

175 mg daily, with or without food. If a patient forgets to take a tablet, and it is within 6 hours of the scheduled time then the patient should be advised to take them as soon as possible. If it is more than 6 hours after the scheduled time, then study medication should not be taken for that day. Study medication should continue as scheduled previously on the subsequent day. A patient should not take more than a single day's dose of tablets, within a day. In the event that the patient cannot hold the tablet(s) down (if the patient vomits) within 30 minutes from taking the tablet(s) or if can identify the tablet (s) in the vomit content, the patient can re-take new tablet(s) from the bottle(s).

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

Dosage and administration details:

1mg 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 daily

Arm title	AI plus placebo

Arm description:

Patients will receive an aromatase inhibitor and a placebo. Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus placebo. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus placebo.

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

Dosage and administration details:

N/A

Number of subjects in period 1	AI plus Saracatinib	AI plus placebo
Started	69	71
Completed	37	58
Not completed	32	13
Adverse event, serious fatal	4	2
Physician decision	12	3
Consent withdrawn by subject	6	2
Adverse event, non-fatal	5	4
Drug discontinued	1	-
Lost to follow-up	1	-
Missing data	-	1
Protocol deviation	3	1

Baseline characteristics

Reporting groups	
Reporting group title	AI plus Saracatinib
Reporting group description:	
Patients will receive an aromatase inhibitor and saracatinib (AZD0530). Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus saracatinib 175 mg daily. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus saracatinib 175 mg daily. Saracatinib (AZD0530) is an oral Src inhibitor and can be administered with or without food.	
Reporting group title	AI plus placebo
Reporting group description:	
Patients will receive an aromatase inhibitor and a placebo. Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus placebo. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus placebo.	

Reporting group values	AI plus Saracatinib	AI plus placebo	Total
Number of subjects	69	71	140
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	36	34	70
From 65-84 years	32	37	69
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	69	71	140
Male	0	0	0
AI sensitivity			
Patient sensitivity to AI: "AI-sensitive/naive": either never previously treated with AI; or if treated with tamoxifen must not have rapid progression on tamoxifen (i.e. treated for >=24 mo adjuvant or >=6 mo in metastatic setting); or, if previously treated with an AI, only in the adjuvant or neo-adjuvant setting AND remained progression free for >=12mo whilst not being treated with an AI. "prior AI": patients NOT meeting criteria above, but previously treated with non-steroidal AI without progression for >=24mo in (neo-) adjuvant setting or for >=6mo for advanced disease.			
Units: Subjects			
AI-sensitive/naive	36	33	69
prior AI	33	38	71

End points

End points reporting groups

Reporting group title	AI plus Saracatinib

Reporting group description:

Patients will receive an aromatase inhibitor and saracatinib (AZD0530). Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus saracatinib 175 mg daily. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus saracatinib 175 mg daily. Saracatinib (AZD0530) is an oral Src inhibitor and can be administered with or without food.

Reporting group title	AI plus placebo

Reporting group description:

Patients will receive an aromatase inhibitor and a placebo. Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus placebo. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus placebo.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population includes any patient who had at least one dose of study medication. There 136 patient in total, with 67 in Arm A (+study drug) and 69 in Arm B (placebo).

Subject analysis set title	Eligible patients
Subject analysis set type	Full analysis

Subject analysis set description:

This population excludes patients with gross eligibility deviations. Patients with gross deviations will be determined in consultation with the Chief Investigator.
Arm A (study drug) has 66 patients, Arm B (placebo) has 68 patients; 134 patients in total.

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This includes all patients randomised into the study regardless of whether they received treatment or not.
Arm A (study drug) has 69 patients; Arm B (placebo) has 71 patients.

Primary: Efficacy (progression free survival)

End point title	Efficacy (progression free survival)

End point description:

Comparison of progression free survival between cohort receiving aromatase inhibition plus saracatinib, versus those receiving aromatase inhibition plus placebo.
The duration of progression-free survival (PFS) is measured as the time from randomisation to the time that confirmed progression or death from any cause is documented (whichever comes first). Patients who neither progress nor die are censored at the date they were last known to be alive and progression free.

End point type	Primary

End point timeframe:

48 months

End point values	AI plus Saracatinib	AI plus placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	67	140	
Units: Patients	69	71	140	

Statistical analyses

Statistical analysis title	Progression-free survival (Cox regression)

Statistical analysis description:

Cox regression to assess whether there is a difference between the treatment and control arm with regards to progression-free survival .

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.955 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.369
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.08
upper limit	1.735
Variability estimate	Standard error of the mean
Dispersion value	0.185

Notes:

[1] - One sided p-value, assessing whether there is reduced risk in the treatment arm.

Secondary: Safety (toxicity)

End point title	Safety (toxicity)

End point description:

Toxicity assessment (e.g. vomiting, cough) based on criteria (CTCAE V4.0) for analysed patients for each assessment.

End point type	Secondary

End point timeframe:

48 months

End point values	AI plus Saracatinib	AI plus placebo	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	67	69	136	
Units: Patients	67	69	136	

Statistical analyses

Statistical analysis title	Fatigue (Mann Whitney U)

Statistical analysis description:

Analysis of whether fatigue is more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.092
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 6
Arm B (placebo): 10

Statistical analysis title	Nausea (Mann Whitney U)

Statistical analysis description:

Analysis of whether nausea is more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.817
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 6
Arm B (placebo): 9

Statistical analysis title	Vomiting (Mann Whitney U)

Statistical analysis description:

Analysis of whether vomiting is more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.016
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 5
Arm B (placebo): 10

Statistical analysis title	Alopecia (Mann Whitney U)

Statistical analysis description:

Analysis of whether alopecia is more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 6
Arm B (placebo): 10

Statistical analysis title	Neuropathy (Mann Whitney U)

Statistical analysis description:

Analysis of whether neuropathy is more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.807
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 6
Arm B (placebo): 10

Statistical analysis title	Mucositis/stomatitis (Mann Whitney U)

Statistical analysis description:

Analysis of whether mucositis/stomatitisis more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.559
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 5
Arm B (placebo): 10

Statistical analysis title	Rash/desquamation (Mann Whitney U)

Statistical analysis description:

Analysis of whether rash/desquamation more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 3
Arm B (placebo): 10

Statistical analysis title	Hypersensitivity (Mann Whitney U)

Statistical analysis description:

Analysis of whether hypersensitivity more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.327
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 6
Arm B (placebo): 10

Statistical analysis title	Anorexia (Mann Whitney U)

Statistical analysis description:

Analysis of whether anorexia more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[10]
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 5
Arm B (placebo): 10

Statistical analysis title	Diarrhoea (Mann Whitney U)

Statistical analysis description:

Analysis of whether diarrhoea more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[11]
P-value	= 0.048
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 4
Arm B (placebo): 10

Statistical analysis title	Constipation (Mann Whitney U)

Statistical analysis description:

Analysis of whether constipation more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[12]
P-value	= 0.87
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 5
Arm B (placebo): 10

Statistical analysis title	Febrile neuropenia (Mann Whitney U)

Statistical analysis description:

Analysis of whether febrile neuropenia more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	= 0.59
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 5
Arm B (placebo): 10

Statistical analysis title	Infection (Mann Whitney U)

Statistical analysis description:

Analysis of whether infection more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[14]
P-value	= 0.275
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - Data was not assessed for the following numbers of patients:
Arm A (study drug): 1
Arm B (placebo): 2

Statistical analysis title	Anaemia (Mann Whitney U)

Statistical analysis description:

Analysis of whether anaemia (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - All patients assessed.

Statistical analysis title	ALT (Mann Whitney U)

Statistical analysis description:

Analysis of whether ALT (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[16]
P-value	= 0.729
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - All patients assessed.

Statistical analysis title	Alkaline phosphatase (Mann Whitney U)

Statistical analysis description:

Analysis of whether alkaline phosphatase (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[17]
P-value	= 0.955
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - All patients assessed.

Statistical analysis title	Phosphate (Mann Whitney U)

Statistical analysis description:

Analysis of whether phosphate (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[18]
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - All patients assessed.

Statistical analysis title	Low sodium (Mann Whitney U)

Statistical analysis description:

Analysis of whether low sodium (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	= 0.626
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - All patients assessed.

Statistical analysis title	High sodium (Mann Whitney U)

Statistical analysis description:

Analysis of whether high sodium (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[20]
P-value	= 0.535
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - All patients assessed.

Statistical analysis title	Low potassium (Mann Whitney U)

Statistical analysis description:

Analysis of whether low potassium (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[21]
P-value	= 0.073
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - All patients assessed.

Statistical analysis title	High potassium (Mann Whitney U)

Statistical analysis description:

Analysis of whether high potassium (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[22]
P-value	= 0.306
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - All patients assessed.

Statistical analysis title	Neutropenia (Mann Whitney U)

Statistical analysis description:

Analysis of whether neutropenia (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	= 0.571
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - All patients assessed.

Statistical analysis title	Thrombocytopenia (Mann Whitney U)

Statistical analysis description:

Analysis of whether thrombocytopenia (as assessed by laboratory testing) more commonly associated with either arm.

Comparison groups	AI plus placebo v AI plus Saracatinib

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[24]
P-value	= 0.438
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - All patients assessed.

Secondary: Efficacy (change in tumour size)

End point title	Efficacy (change in tumour size)

End point description:

Change in tumour size (as captured by the sum of diameters measurement that informs the RECIST v1.1 response).

End point type	Secondary

End point timeframe:

48 months

End point values	AI plus Saracatinib	AI plus placebo	Eligible patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39[25]	57[26]	96[27]	
Units: Number of reductions	39	57	96	

Notes:

[25] - 30 patients had missing measurement data, so % reduction in tumour size could not be calculated.
[26] - 14 patients had missing measurement data, so % reduction in tumour size could not be calculated.
[27] - 44 patients had missing measurement data, so % reduction in tumour size could not be calculated.

Statistical analyses

Statistical analysis title	Change in sum of tumour diameters (Mann Whitney U)

Statistical analysis description:

Assessing whether there is a significant difference in the percentage reduction in tumour size across arms.

Comparison groups	AI plus Saracatinib v AI plus placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.484
Method	Wilcoxon (Mann-Whitney)

Secondary: Efficacy (overall survival)

End point title	Efficacy (overall survival)

End point description:

Comparison of overall survival between cohort receiving aromatase inhibition plus saracatinib, versus those receiving aromatase inhibition plus placebo. Overall Survival is defined as the time from the date of randomisation to the date of death from any cause. Patients who do not die are censored at the date

they were last known to be alive.

End point type	Secondary

End point timeframe:

48 months

End point values	AI plus Saracatinib	AI plus placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Patients	69	71		

Statistical analyses

Statistical analysis title	Overall survival (Cox regression)

Statistical analysis description:

Cox regression to assess whether there is a difference between the treatment and control arm with regards to overall survival .

Comparison groups	AI plus Saracatinib v AI plus placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.881 [28]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.322
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.976
upper limit	1.791
Variability estimate	Standard error of the mean
Dispersion value	0.237

Notes:

[28] - One sided p-value, assessing whether there is reduced risk in the treatment arm.

Secondary: Efficacy (response)

End point title	Efficacy (response)

End point description:

Change in tumour response (as captured by the number of patients exhibiting a complete or partial responss using the RECIST v1.1 criteria).

End point type	Secondary

End point timeframe:

48 months

End point values	AI plus Saracatinib	AI plus placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44[29]	59[30]	103[31]	
Units: Patients	44	59	103	

Notes:

[29] - 25 patients had missing RECIST response.

[30] - 20 patients had missing RECIST response.

[31] - 37 patients had missing RECIST response.

Statistical analyses

Statistical analysis title	Difference in RECIST response

Statistical analysis description:

Calculating the difference in % complete/partial response in each arm.

Comparison groups	AI plus Saracatinib v AI plus placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other[32]
Parameter estimate	Mean difference (net)
Point estimate	19.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	7.5
upper limit	30.7

Notes:

[32] - Not an analysis as such - just a calculation of the difference in the means. Note that the mean difference is calculated as Arm B-Arm A (i.e., Placebo - study drug).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AE reported from consent signing to 30 days after final study treatment (exception: events considered unrelated before starting study drug). AEs occuring >30 days after final study treatment considred related to study drug will be reported to CSA.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	AI plus Saracatinib

Reporting group description:

Patients will receive an aromatase inhibitor and saracatinib (AZD0530). Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus saracatinib 175 mg daily. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus saracatinib 175 mg daily. Saracatinib (AZD0530) is an oral Src inhibitor and can be administered with or without food.

Reporting group title	AI plus placebo

Reporting group description:

Patients will receive an aromatase inhibitor and a placebo. Patients will be enrolled into one of two strata: an "AI-sensitive/naïve" group of patients with potentially AI-sensitive tumours, and a second "prior-AI" group of women whose cancers have already progressed on an AI, but for whom there is likely to still be some endocrine sensitivity. For women in the "AI-sensitive/naïve" group, treatment would be with anastrazole 1mg daily plus placebo. For women in the "prior AI" group, treatment would be exemestane 25mg daily plus placebo.

Serious adverse events	AI plus Saracatinib	AI plus placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 67 (44.78%)	14 / 69 (20.29%)	
number of deaths (all causes)	39	41	
number of deaths resulting from adverse events			
Vascular disorders			
Bilateral Pulmonary Emboli			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver portal vein thrombosis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 67 (5.97%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi organ failure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 67 (5.97%)	4 / 69 (5.80%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Ejection fraction decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Back pain (radiating)			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low haemoglobin			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood in diarrhoea			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 67 (4.48%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Ascites			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma glutamyl transferase			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
High bilirubin			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin lesions/rash			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Derranged renal U+E			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankle fracture			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain (musculoskeletal)			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 67 (2.99%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Joint pain			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus aureus infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AI plus Saracatinib	AI plus placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 67 (83.58%)	46 / 69 (66.67%)	
Investigations			
ALT	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Alkaline phosphatase	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	3 / 67 (4.48%)	11 / 69 (15.94%)	
occurrences (all)	3	11	
Phosphate	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	27 / 67 (40.30%)	4 / 69 (5.80%)	
occurrences (all)	27	4	
Low sodium	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	0 / 67 (0.00%)	4 / 69 (5.80%)	
occurrences (all)	0	4	
Low potassium	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		

subjects affected / exposed	7 / 67 (10.45%)	2 / 69 (2.90%)	
occurrences (all)	7	2	
High potassium	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Neutropenia	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	3 / 67 (4.48%)	3 / 69 (4.35%)	
occurrences (all)	3	3	
Thrombocytopenia	Additional description: Abnormal results of laboratory values. Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	
occurrences (all)	0	2	
Nervous system disorders			
Neuropathy	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	30 / 67 (44.78%)	20 / 69 (28.99%)	
occurrences (all)	30	20	
Gastrointestinal disorders			
Nausea	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	17 / 67 (25.37%)	8 / 69 (11.59%)	
occurrences (all)	17	8	
Vomiting	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	6 / 67 (8.96%)	1 / 69 (1.45%)	
occurrences (all)	6	1	
Mucositis/Stomatitis	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Diarrhoea	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	10 / 67 (14.93%)	3 / 69 (4.35%)	
occurrences (all)	10	3	
Constipation	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	6 / 67 (8.96%)	4 / 69 (5.80%)	
occurrences (all)	6	4	

Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Rash/desquamation	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	6 / 67 (8.96%)	1 / 69 (1.45%)	
occurrences (all)	6	1	
Infections and infestations			
Infection	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	18 / 67 (26.87%)	20 / 69 (28.99%)	
occurrences (all)	18	20	
Metabolism and nutrition disorders			
Anorexia	Additional description: Defining "affected" as CTCAE Grade 2 or above.		
subjects affected / exposed	8 / 67 (11.94%)	3 / 69 (4.35%)	
occurrences (all)	8	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2011	• Patient Flyer V1.0 • Sponsor letter 5th May 2011 • GP Letter V1.0 • CI CV • Investigator Brochure Ed9 • Patient Invite Letter V1.0 • PIS Main trial V1.0 • ICF Main trial V1.0 • PIS Sub-study V1.0 • ICF Sub-study V1.0 • Protocol V1.0 • REC Application
10 February 2012	• CPAS comments • PIS Main trial V1.1 • ICF Main trial V1.1 • PIS Sub-study V1.1 • ICF Sub-study V1.1 • GP Letter & attachment V1.1 • Patient Flyer V1.1 • Summary PIS V1.0 • Patient Invite Letter V1.1 • Protocol V1.1
15 March 2012	• Summary PIS V1.1
09 May 2012	• Addition of site 005, 018, 008 & 011. • Removal of Addenbrooke's Hospital & Queen Elizabeth Hospital, Woolich, Southend Hospital & Queen Elizabeth Hospital, Birmingham.
24 July 2012	• Addition of site 019. • Change of PI at site 011.
06 November 2012	• Addition of site 020.
10 December 2012	• Emergency ID Cards
21 March 2013	• Eligibility Flowchart
30 April 2013	• Screening Feedback Form v1.0
17 October 2014	• Updated CMC and Manufacturing Authorisation
06 November 2014	• Temporary halt of recruitment at St.Barts London

24 November 2014	• Change of site name and Trust for 007. • Change of PI, site name and Trust for 020. • Removal of site 017.
19 February 2015	• Dosing Instruction Card
28 April 2016	• Change of PI at sites 16, 21 & 22
25 October 2016	• Change of PI at site 008

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported