Clinical trial results:
A Phase II study to assess the safety and efficacy of the steroid sulfatase inhibitor Irosustat when added to an aromatase inhibitor in ER positive locally advanced or metastatic breast cancer patients.

Summary

EudraCT number	2011-005680-25
Trial protocol	GB
Global end of trial date	17 December 2014

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016
Summary attachment (see zip file)	IRIS Clinical Study Report Summary 230316 (IRIS Clinical Study Report Summary 230316.pdf)

Trial information

Trial identification

Sponsor protocol code	C/22/2011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01785992
WHO universal trial number (UTN)	-
Other trial identifiers	Funder Reference (Cancer Research UK): C20208/A13392, IPSEN Study Protocol Number: X-52-58064-010

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Room 215 Level 2, Medical School Building Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Professor Carlo Palmieri, University of Liverpool, 0044 151 706 3616, C.Palmieri@liverpool.ac.uk
Scientific contact	Professor Carlo Palmieri, University of Liverpool, 0044 151 706 3616, C.Palmieri@liverpool.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	04 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2014
Global end of trial reached?	Yes
Global end of trial date	17 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess if adding Irosustat to existing aromatase inhibitor (AI) treatment in patients who have progressed on an AI can control cancer growth by either stopping its growth or reducing its size for a period of 6 months.

Protection of trial subjects:

At study conception three known drug-related adverse events were identified as requiring specific inclusion/exclusion criteria and/or monitoring throughout the study:
1. Muscoskeletal Side Effects: Regular assessments of Calcium, Phosphate and Magnesium levels were included in the standard clinical chemistry bloods and were monitored regularly.
2. Renal Toxicity: Patients with serum creatinine ≥1.5 x ULN were excluded from the study. Serum urea and creatinine were included in the standard clinical chemistry bloods and were monitored regularly.
3. Cardio Toxicity: Patients with a history of prolonged QT or a prolonged QT at baseline were excluded from the study. ECG activity and blood pressure were routinely monitored.
Expected adverse events relating to study treatment were summarised in the patient information sheet.

As per protocol, an interim analysis was conducted after 13 patients had completed study treatment, the protocol specified that if none of these patients had responded to treatment (complete response, partial response, stable disease) the study would stop. After review of the efficacy and safety data the IDMC recommended that the study continue without change.

Background therapy:

This trial recruited postmenopausal women with ER positive locally advanced or metastatic breast cancer who have progressed during 1st line treatment with an Aromatase Inhibtior (AI). Eligible patients who were enrolled on the study continued to take the class of AI on which they progressed (either Anastrazole (1mg o.d), Letrozole (2.5mg o.d) or Exemestane (25mg o.d)) in addition to the study drug (Irusostat). AIs were considered to be a non-Investigational Medicinal Product (NIMP).

Concomitant medications could be prescribed at the treating physicians discretion, with the exception of prohibited medications described in the study protocol. Concomitant medications (and the reason for the medication) were recorded in the study database for the period 4-weeks prior to starting study treatment until the patient's last study visit.

Evidence for comparator:

Not Applicable

Actual start date of recruitment	06 February 2013
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: 28

Worldwide total number of subjects	28
EEA total number of subjects	28

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)	15
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Nine UK sites were opened to recruitment, six of these enrolled patients to the study. The first site opened to recruitment on 22/10/2012 and the first patient consent was on 06/02/2013 with the patient confirmed as eligible to enroll into the study on 09/02/2015; the last patient consent was on 26/02/2014 with study enrollment on 05/03/2014.

Pre-assignment

Screening details:

28 patients were consented to the study. 1 patient was found to be ineligible, due to not meeting the cardiac criteria. The remaining 27 patients were all enrolled on the trial.

Pre-assignment period milestones

Number of subjects started	28
Number of subjects completed	27

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible: 1

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:

Not Applicable

Arms

Arm title	Intervention

Arm description: -

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

Dosage and administration details:

40mg once daily (O.D) until disease progression, unacceptable toxicity or withdrawal.

Number of subjects in period 1[1]	Intervention
Started	27
Completed	23
Not completed	4
Physician decision	1
Consent withdrawn by subject	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient was found to be ineligible so did not start study treatment. She has not been included int he baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
All patients enrolled on the trial	

Reporting group values	Overall Trial	Total	
Number of subjects	27	27	
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	63.7		
standard deviation	± 10.5	-	
Gender categorical			
Only female patients were eligible			
Units: Subjects			
Female	27	27	
Male	0	0	
Ethnicity Units: Subjects			
White	24	24	
Mixed	0	0	
Asian	1	1	
Black	1	1	
Chinese	1	1	
Other	0	0	
Treatment History: Prior Chemotherapy			
Patients may have had multiple lines of chemotherapy (i.e. in neoadjuvant, adjuvant and/or advanced 1st line).			
Units: Subjects			
No prior chemotherapy	10	10	
Prior chemotherapy	17	17	
Treatment History: Prior Radiotherapy			
Patients may have had radiotherapy in the adjuvant and/or palliative setting			
Units: Subjects			
No Prior Radiotherapy	13	13	
Prior Radiotherapy	14	14	

Treatment History: Prior Endocrine Therapy			
Patients may have had endocrine therapy in any setting (i.e. neoadjuvant, adjuvant and/or advanced 1st line).			
Units: Subjects			
No prior endocrine therapy	0	0	
Prior endocrine therapy	27	27	
Treatment History: Breast Cancer Surgery Units: Subjects			
None	7	7	
Yes	20	20	
Tumour Type Units: Subjects			
Invasive Ductal Carcinoma	20	20	
Invasive Lobular Carcinoma	4	4	
Invasive Mixed Carcinoma	1	1	
Other Specified Invasive Histology	1	1	
Unable to Classify	1	1	
Nodal Status Units: Subjects			
N0	2	2	
N1	12	12	
N2	1	1	
N3	1	1	
NX	4	4	
Not Appliable	6	6	
Not Known	1	1	
Primary Cancer Stage Units: Subjects			
Stage I	4	4	
Stage II	10	10	
Stage III	3	3	
Stage IV	2	2	
Not Applicable	6	6	
Not Known	1	1	
Not Done	1	1	
Primary Tumour Grade Units: Subjects			
Grade 1	3	3	
Grade 2	12	12	
Grade 3/4	5	5	
Not Applicable	4	4	
Not Known	3	3	
Progesterone receptor (PgR) Status Units: Subjects			
Positive	12	12	
Negative	5	5	
Not Applicable	5	5	
Not Known	5	5	
HER2 Status Units: Subjects			

Zero	6	6	
1+	8	8	
2+	2	2	
Not Done	6	6	
Not Applicable	5	5	
Type of 1st Breast Cancer Relapse Units: Subjects			
Local Recurrence	0	0	
Distant Recurrence / Metastatic	26	26	
Not Done	1	1	
Body Mass Index Units: kg/m2			
median	28.1		
standard deviation	± 6.3	-	
Primary Tumour Size			
Longest Diameter Data provided for N=17 in overall trial and N=15 in per protocol analysis			
Units: mm			
median	28		
full range (min-max)	15 to 120	-	
Duration of AI treatment at enrolment			
Duration of treatment with aromatase inhibitor at study enrolment			
Units: Months			
median	21.1		
inter-quartile range (Q1-Q3)	13.3 to 37.6	-	
Time from primary diagnosis to metastatic diagnosis			
Based on diagnositc biopsy result. N=23 in overall trial; N=19 in per-protocol analysis			
Units: Months			
median	60.7		
inter-quartile range (Q1-Q3)	2 to 116.1	-	

Subject analysis sets

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Patients evaulable for efficacy endpoints (i.e. had at least one tumour assessment on study drug; or death (due to breast cancer) prior to tumour assessment)

Reporting group values	Per Protocol		
Number of subjects	23		
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 standard deviation	 63.3 ± 9.9		
Gender categorical			
Only female patients were eligible			
Units: Subjects			
Female Male	23 0		
Ethnicity Units: Subjects			
White Mixed Asian Black Chinese Other	21 0 1 0 1 0		
Treatment History: Prior Chemotherapy			
Patients may have had multiple lines of chemotherapy (i.e. in neoadjuvant, adjuvant and/or advanced 1st line).			
Units: Subjects			
No prior chemotherapy Prior chemotherapy	9 14		
Treatment History: Prior Radiotherapy			
Patients may have had radiotherapy in the adjuvant and/or palliative setting			
Units: Subjects			
No Prior Radiotherapy Prior Radiotherapy	11 12		
Treatment History: Prior Endocrine Therapy			
Patients may have had endocrine therapy in any setting (i.e. neoadjuvant, adjuvant and/or advanced 1st line).			
Units: Subjects			
No prior endocrine therapy Prior endocrine therapy	0 23		
Treatment History: Breast Cancer Surgery Units: Subjects			
None Yes	6 17		
Tumour Type Units: Subjects			
Invasive Ductal Carcinoma Invasive Lobular Carcinoma Invasive Mixed Carcinoma Other Specified Invasive Histology Unable to Classify	16 4 1 1 1		
Nodal Status			

Units: Subjects			
N0	2		
N1	10		
N2	1		
N3	1		
NX	2		
Not Appliable	6		
Not Known	1		
Primary Cancer Stage Units: Subjects			
Stage I	4		
Stage II	10		
Stage III	1		
Stage IV	1		
Not Applicable	6		
Not Known	0		
Not Done	1		
Primary Tumour Grade Units: Subjects			
Grade 1	3		
Grade 2	8		
Grade 3/4	5		
Not Applicable	4		
Not Known	3		
Progesterone receptor (PgR) Status Units: Subjects			
Positive	9		
Negative	4		
Not Applicable	5		
Not Known	5		
HER2 Status Units: Subjects			
Zero	6		
1+	5		
2+	1		
Not Done	6		
Not Applicable	5		
Type of 1st Breast Cancer Relapse Units: Subjects			
Local Recurrence	0		
Distant Recurrence / Metastatic	22		
Not Done	1		
Body Mass Index Units: kg/m2			
median	28.2		
standard deviation	± 6.6		
Primary Tumour Size			
Longest Diameter Data provided for N=17 in overall trial and N=15 in per protocol analysis			
Units: mm			
median	25		

full range (min-max)	15 to 46		
Duration of AI treatment at enrolment			
Duration of treatment with aromatase inhibitor at study enrolment			
Units: Months median inter-quartile range (Q1-Q3)	 21.1 10.3 to 35.7		
Time from primary diagnosis to metastatic diagnosis			
Based on diagnositc biopsy result. N=23 in overall trial; N=19 in per-protocol analysis			
Units: Months median inter-quartile range (Q1-Q3)	 60.7 2 to 105.4		

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: -	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Patients evaulable for efficacy endpoints (i.e. had at least one tumour assessment on study drug; or death (due to breast cancer) prior to tumour assessment)

Primary: Clinical Benefit Rate - Local RECIST Review

End point title	Clinical Benefit Rate - Local RECIST Review[1]

End point description:

Clinical Benefit Rate is defined as Complete Response (CR), Partial Response (PR) or Stable Disease (SD) by Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1).

The primary endpoint has been reported based on local site RECIST review.

End point type	Primary

End point timeframe:

6 months

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: This study is a one arm design. Therefore the statistical analysis does not have more than one comparison arm. The EudraCT system would not allow statistical analysis details to be completed without defining a second comparison arm, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	23		
Units: percent				
median (confidence interval 95%)	18.5 (6.3 to 38.1)	21.7 (7.4 to 43.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Benefit Rate - Central RECIST Review

End point title	Clinical Benefit Rate - Central RECIST Review[2]

End point description:

Clinical Benefit Rate is defined as Complete Response (CR), Partial Response (PR), or Stable Disease (SD) by Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1).

This has been reported by central RECIST review.

End point type	Primary

End point timeframe:

6 months

Notes:

[2] - 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: This study is a one arm design. Therefore the statistical analysis does not have more than one comparison arm. The EudraCT system would not allow statistical analysis details to be completed without defining a second comparison arm, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	23		
Units: percent				
median (confidence interval 95%)	14.8 (4.2 to 33.7)	17.4 (5 to 38.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Clinical Benefit

End point title	Duration of Clinical Benefit

End point description:

End point type	Secondary

End point timeframe:

End of treatment

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26[3]	23		
Units: No Days				
median (inter-quartile range (Q1-Q3))	77.5 (66 to 139)	80 (75 to 160)		

Notes:

[3] - For one patient start date of study drug is not known

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective Response Rate is defined as Complete Response (CR) or Partial Response (PR), as per Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1)

End point type	Secondary

End point timeframe:
End of treatment

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	23		
Units: Number of Patients				
Complete Response	0	0		
Partial Response	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Secondary

End point timeframe:
First evidence of progression or death due to any cause

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	23		
Units: Months				
median (confidence interval 95%)	2.7 (2.5 to 4.6)	2.7 (2.5 to 4.6)		

Attachments (see zip file)	PFS Graph/PFS Graph for EudraCT Submission 220316.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormones - Andrstenedione

End point title	Circulating Steroid Hormones - Andrstenedione

End point description:

End point type	Secondary

End point timeframe:

Samples were collected monthly for the duration of a patients participation on study up to 6 months

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24[4]	21[5]		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Baseline	59.5 (46.8 to 78.2)	57 (46 to 77)		
Month 1	35 (28.5 to 55)	36 (28 to 56)		
Month 2	44 (41 to 63)	44 (41 to 63)		
Month 3	46 (30.5 to 55.5)	46 (30.5 to 55.5)		
Month 4	36 (30.5 to 52)	36 (30.5 to 52)		
Month 5	23 (21 to 29)	23 (21 to 29)		
Month 6	36 (31.5 to 42)	36 (31.5 to 42)		

Notes:

[4] - Baseline N=24; Month 1 N=23; Month 2 N = 21; Month 3 N=19; Month 4 N=7; Month 5 N=7; Month 6 N=4.

[5] - Baseline N=21; Month 1 N=21; Month 2 N = 21; Month 3 N=19; Month 4 N=7; Month 5 N=7; Month 6 N=4.

Attachments (see zip file)	SH Graphs/SH Graphs for EudraCT Submision 220316.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormones - Oestrone Sulphate

End point title	Circulating Steroid Hormones - Oestrone Sulphate

End point description:

End point type	Secondary

End point timeframe:

Samples were collected monthly for the duration of a patients participation on study

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26[6]	23[7]		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Basline	40 (40 to 70.8)	40 (40 to 64.5)		
Month 1	40 (40 to 70)	40 (40 to 70)		
Month 2	40 (40 to 81)	40 (40 to 81)		
Month 3	40 (40 to 53.5)	40 (40 to 53.5)		
Month 4	40 (40 to 158)	40 (40 to 158)		

Month 5	65 (40 to 152.5)	65 (40 to 152.5)		
Month 6	61 (57 to 113.8)	61 (57 to 113.8)		

Notes:

[6] - Baseline N=26; Month 1 N=26; Month 2 N = 21; Month 3 N=20; Month 4 N=7; Month 5 N=7; Month 6 N=6.

[7] - Baseline N=23; Month 1 N=23; Month 2 N = 21; Month 3 N=20; Month 4 N=7; Month 5 N=7; Month 6 N=6.

Attachments (see zip file)	SH Graphs/SH Graphs for EudraCT Submision 220316.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormones - Dehydroepiandrosterone (DHEA)

End point title	Circulating Steroid Hormones - Dehydroepiandrosterone (DHEA)

End point description:

End point type	Secondary

End point timeframe:

Samples were collected monthly for the duration of a patients participation on study

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24[8]	21[9]		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Basline	118.5 (77.5 to 194)	114 (80 to 172)		
Month 1	84.5 (56 to 137.2)	84.5 (59 to 134.5)		
Month 2	83 (43 to 155)	83 (43 to 155)		
Month 3	62.5 (47.8 to 105.8)	62.5 (47.8 to 105.8)		
Month 4	56 (40.5 to 73)	56 (40.5 to 73)		
Month 5	69 (48 to 75)	69 (48 to 75)		
Month 6	53 (26.8 to 77.8)	53 (26.8 to 77.8)		

Notes:

[8] - Baseline N=24; Month 1 N=24; Month 2 N = 21; Month 3 N=20; Month 4 N=7; Month 5 N=7; Month 6 N=6.

[9] - Baseline N=21; Month 1 N=22; Month 2 N = 21; Month 3 N=20; Month 4 N=7; Month 5 N=7; Month 6 N=6.

Attachments (see zip file)	SH Graphs/SH Graphs for EudraCT Submision 220316.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormones - Dehydroepiandrosterone Sulphate (DHEAS)

End point title	Circulating Steroid Hormones - Dehydroepiandrosterone Sulphate (DHEAS)

End point description:

End point type	Secondary

End point timeframe:

Samples were collected monthly for the duration of a patients participation on study

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23[10]	21[11]		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Baseline	64 (51 to 98.5)	64 (50 to 92)		
Month 1	149.5 (104 to 196.8)	151 (10.3 to 199)		
Month 2	135 (73.5 to 175)	135 (73.5 to 175)		
Month 3	146 (46 to 188)	146 (46 to 188)		
Month 4	84 (76 to 126.5)	84 (76 to 126.5)		
Month 5	103 (81.2 to 151.8)	103 (81.2 to 151.8)		
Month 6	124 (74 to 187)	124 (74 to 187)		

Notes:

[10] - Baseline N=22; Month 1 N=223; Month 2 N = 19; Month 3 N=17; Month 4 N=7; Month 5 N=4; Month 6 N=5.

[11] - Baseline N=21; Month 1 N=21; Month 2 N = 19; Month 3 N=17; Month 4 N=7; Month 5 N=4; Month 6 N=5.

Attachments (see zip file)	SH Graphs/SH Graphs for EudraCT Submision 220316.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormones - DHEA to DHEAS ratio

End point title	Circulating Steroid Hormones - DHEA to DHEAS ratio

End point description:

End point type	Secondary

End point timeframe:

Samples were collected monthly for the duration of a patients participation on study

End point values	Per Protocol			
Subject group type	Subject analysis set			
Number of subjects analysed	21[12]			
Units: Ratio				
median (inter-quartile range (Q1-Q3))				
Baseline	2 (1.2 to 2.5)			
Month 1	0.7 (0.4 to 1.3)			
Month 2	0.9 (0.5 to 1)			
Month 3	0.7 (0.5 to 1)			
Month 4	0.6 (0.3 to 1)			
Month 5	0.7 (0.3 to 0.9)			
Month 6	0.4 (0.3 to 0.9)			

Notes:

[12] - Baseline N=21; Month 1 N=20; Month 2 N = 19; Month 3 N=17; Month 4 N=7; Month 5 N=4; Month 6 N=5.

Attachments (see zip file)	SH Graphs/SH Graphs for EudraCT Submision 220316.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormones - Testosterone

End point title	Circulating Steroid Hormones - Testosterone

End point description:

End point type	Secondary

End point timeframe:

Samples were collected monthly for the duration of a patients participation on study

End point values	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21[13]	20[14]		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Basline	12 (8 to 21)	12.5 (8 to 21.2)		
Month 1	10.5 (8.8 to 15.2)	10.5 (8.8 to 15.2)		
Month 2	11 (6 to 15)	11 (6 to 15)		
Month 3	11.5 (6.2 to 17.2)	11.5 (6.2 to 17.2)		
Month 4	8.5 (6 to 12.5)	8.5 (6 to 12.5)		
Month 5	8 (3.5 to 12.2)	8 (3.5 to 12.2)		
Month 6	5 (4 to 10)	5 (4 to 10)		

Notes:

[13] - Baseline N=21; Month 1 N=16; Month 2 N = 17; Month 3 N=14; Month 4 N=6; Month 5 N=4; Month 6 N=5.

[14] - Baseline N=20; Month 1 N=16; Month 2 N = 17; Month 3 N=14; Month 4 N=6; Month 5 N=4;

Month 6 N=5.

Attachments (see zip file)	SH Graphs/SH Graphs for EudraCT Submision 220316.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from the time a patient signed informed consent until the end of follow-up. AEs were followed-up according to local practice until the event has stabilised or resolved, or until the last follow-up visit, whichever was sooner

Adverse event reporting additional description:

AEs were reviewed at every patient visit.

Disease progression was not classed as an AE.

AEs we assessed for severity (NCI CTCAE v4.03) and causality by the local PI; the CI provided an assessment for SAEs. All AEs were recorded in the study EDC system.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Full Analysis Set

Reporting group description:

All patients who received at least one dose of study medication

Serious adverse events	Full Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 27 (22.22%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Lower respiratory tract infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nausea, Vomiting, Fever			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Full Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Vascular disorders			

Haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Surgical and medical procedures			
Pleurodesis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Death			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	12 / 27 (44.44%)		
occurrences (all)	15		
Gravitational oedema			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	7		
Oedema			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Pain			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Breast ulceration			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Blood glucose			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Haemoglobin			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Cardiac disorders			
Dizziness			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Bundle branch block			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nervous system disorders			
Circadian rhythm sleep disorder			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Headache			

subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 7		
Insomnia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Constipation subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4		
Diarrhoea subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 8		
Dry mouth subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Dyspepsia			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	12 / 27 (44.44%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	20 / 27 (74.07%)		
occurrences (all)	28		
Rash			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	6		
Rash erythematous			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Rash generalised			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Stress urinary incontinence			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Back pain			

subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	3		
Bursitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Pain in jaw			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		

Pneumonia subjects affected / exposed occurrences (all) Sepsis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 1 / 27 (3.70%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 7 1 / 27 (3.70%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2012	Substantial Amendments: 1. Safety visit timeline. 2. End of trial definition. 3. Updated Investigator's Brochure. 4. Addition of ALP and Creatinine Clearance assessments to every study visit (study protocol).
30 October 2013	Substantial Amendments: 1. The removal of the collection of blood for the steroid sulfatase (STS) activity analysis from the IRIS protocol and PIS. 2. Change in Contact details for the Chief Investigator. 3. Confirmation of the definition of progression free survival. 4. Clarification of the inclusion criteria defining the previous response to the aromatase inhibitor (AI) required for entry into the trial. 5. Change in the inclusion criteria stating the definition of postmenopausal. 6. Change in the exclusion criterion stating that the AI must not be discontinued prior to study entry. 7. Confirmation of the timing of the post treatment visit within the definition of the early discontinuation of the study. 8. Update of additional expected adverse events defined by the investigator brochure for Irosustat v6.0.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported