



## 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
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#### 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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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. Musculoskeletal 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  $\geq 1.5 \times$  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 Inhibitor (AI). Eligible patients who were enrolled on the study continued to take the class of AI on which they progressed (either Anastrozole (1mg o.d), Letrozole (2.5mg o.d) or Exemestane (25mg o.d)) in addition to the study drug (Irosustat). 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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 28
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Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

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**Subjects enrolled per age group**

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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
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### 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

<b>Arm title</b>	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.

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Consent withdrawn by subject	3

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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 in the 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 Applicable	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	
<b>Type of 1st Breast Cancer Relapse</b>			
Units: Subjects			
Local Recurrence	0	0	
Distant Recurrence / Metastatic	26	26	
Not Done	1	1	
<b>Body Mass Index</b>			
Units: kg/m <sup>2</sup>			
median	28.1		
standard deviation	± 6.3	-	
<b>Primary Tumour Size</b>			
<b>Longest Diameter</b>			
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	-	
<b>Duration of AI treatment at enrolment</b>			
<b>Duration of treatment with aromatase inhibitor at study enrolment</b>			
Units: Months			
median	21.1		
inter-quartile range (Q1-Q3)	13.3 to 37.6	-	
<b>Time from primary diagnosis to metastatic diagnosis</b>			
Based on diagnostic 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 evaluable for efficacy endpoints (i.e. had at least one tumour assessment on study drug; or death (due to breast cancer) prior to tumour assessment)

<b>Reporting group values</b>	Per Protocol		
Number of subjects	23		
<b>Age categorical</b>			
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	63.3		
standard deviation	± 9.9		
Gender categorical			
Only female patients were eligible			
Units: Subjects			
Female	23		
Male	0		
Ethnicity			
Units: Subjects			
White	21		
Mixed	0		
Asian	1		
Black	0		
Chinese	1		
Other	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	9		
Prior chemotherapy	14		
Treatment History: Prior Radiotherapy			
Patients may have had radiotherapy in the adjuvant and/or palliative setting			
Units: Subjects			
No Prior Radiotherapy	11		
Prior Radiotherapy	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	0		
Prior endocrine therapy	23		
Treatment History: Breast Cancer Surgery			
Units: Subjects			
None	6		
Yes	17		
Tumour Type			
Units: Subjects			
Invasive Ductal Carcinoma	16		
Invasive Lobular Carcinoma	4		
Invasive Mixed Carcinoma	1		
Other Specified Invasive Histology	1		
Unable to Classify	1		
Nodal Status			

Units: Subjects			
N0	2		
N1	10		
N2	1		
N3	1		
NX	2		
Not Applicable	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/m <sup>2</sup>			
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	21.1		
inter-quartile range (Q1-Q3)	10.3 to 35.7		
Time from primary diagnosis to metastatic diagnosis			
Based on diagnostic 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 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 evaluable 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 <sup>[1]</sup>
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 <sup>[2]</sup>
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.

<b>End point values</b>	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

<b>End point values</b>	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26 <sup>[3]</sup>	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

<b>End point values</b>	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

<b>End point values</b>	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 - Andrstedione

End point title | Circulating Steroid Hormones - Andrstedione

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

<b>End point values</b>	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24 <sup>[4]</sup>	21 <sup>[5]</sup>		
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.

<b>Attachments (see zip file)</b>	SH Graphs/SH Graphs for EudraCT Submission 220316.pdf
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### 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	

<b>End point values</b>	Intervention	Per Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26 <sup>[6]</sup>	23 <sup>[7]</sup>		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Baseline	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.

<b>Attachments (see zip file)</b>	SH Graphs/SH Graphs for EudraCT Submission 220316.pdf
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### 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 <sup>[8]</sup>	21 <sup>[9]</sup>		
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.

<b>Attachments (see zip file)</b>	SH Graphs/SH Graphs for EudraCT Submission 220316.pdf
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### 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)
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End point description:

End point type	Secondary
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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 <sup>[10]</sup>	21 <sup>[11]</sup>		
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.

<b>Attachments (see zip file)</b>	SH Graphs/SH Graphs for EudraCT Submission 220316.pdf
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**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
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End point description:

End point type	Secondary
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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 <sup>[12]</sup>			
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.

<b>Attachments (see zip file)</b>	SH Graphs/SH Graphs for EudraCT Submission 220316.pdf
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### 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 <sup>[13]</sup>	20 <sup>[14]</sup>		
Units: ng/dl				
median (inter-quartile range (Q1-Q3))				
Baseline	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.

<b>Attachments (see zip file)</b>	SH Graphs/SH Graphs for EudraCT Submission 220316.pdf
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### **Statistical analyses**

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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
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

### Reporting groups

Reporting group title	Full Analysis Set
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Reporting group description:

All patients who received at least one dose of study medication

<b>Serious adverse events</b>	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 %

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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2012	Substantial Amendments: <ol style="list-style-type: none"><li>1. Safety visit timeline.</li><li>2. End of trial definition.</li><li>3. Updated Investigator's Brochure.</li><li>4. Addition of ALP and Creatinine Clearance assessments to every study visit (study protocol).</li></ol>
30 October 2013	Substantial Amendments: <ol style="list-style-type: none"><li>1. The removal of the collection of blood for the steroid sulfatase (STS) activity analysis from the IRIS protocol and PIS.</li><li>2. Change in Contact details for the Chief Investigator.</li><li>3. Confirmation of the definition of progression free survival.</li><li>4. Clarification of the inclusion criteria defining the previous response to the aromatase inhibitor (AI) required for entry into the trial.</li><li>5. Change in the inclusion criteria stating the definition of postmenopausal.</li><li>6. Change in the exclusion criterion stating that the AI must not be discontinued prior to study entry.</li><li>7. Confirmation of the timing of the post treatment visit within the definition of the early discontinuation of the study.</li><li>8. Update of additional expected adverse events defined by the investigator brochure for Irosustat v6.0.</li></ol>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported