Clinical trial results:
A phase II, open label, preoperative study to assess the efficacy of the novel steroid sulfatase inhibitor Irosustat in postmenopausal women with early oestrogen receptor positive breast cancer.

Summary

EudraCT number	2011-005240-10
Trial protocol	GB
Global end of trial date	26 November 2014

Results information

Result version number	v1 (current)
This version publication date	23 March 2016
First version publication date	23 March 2016

Trial information

Trial identification

Sponsor protocol code	C/24/2011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01662726
WHO universal trial number (UTN)	-
Other trial identifiers	Ipsen Study Protocol Number: X-52-58064-011

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	28 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2014
Global end of trial reached?	Yes
Global end of trial date	26 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study will use 3'-deoxy-3'-[18F]Fluorothymidine Positron Emission Tomography (FLT-PET) to assess the ability of a novel endocrine treatment for breast cancer, Irosustat, to slow down cancer cell growth.

Protection of trial subjects:

At protocol conception three main areas of risk were identified as requiring specific inclusion/exclusion criteria and/or monitoring throughout the study:

1. Known adverse events: Muscoskeletal side effects, renal toxicity and cardiac toxicity were identified from previous studies as requiring specific inclusion/exclusion criteria and monitoring throughout the study. These were addressed in the study protocol, and patients were fully-informed of the known adverse events associated with Irosustat.

2. Possible drug interactions: Advice was provided in the protocol as potential for Irosustat to induce drug-drug interactions through inhibition or induction of CYP450 isoenzymes. The protocol included details of medications that were not permitted whilst on study treatment, and medications for which caution and additional monitoring should be applied if administered in conjunction with Irosustat.

3. Radiation Exposure: The total amount of radiation received in this study was equivalent to the total amount of natural background radioactivity that one would have received over the past seven and a half years by being resident in the UK. These exposures are considered very unlikely to put the patients' health at risk.

An independent, combined Trial Steering Committee/Data Monitoring Committee was convened to oversee the trial.

Background therapy:

There were no protocol-specified background therapies.

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 from consent until the patient's last study visit.

Evidence for comparator:

Not applicable - this was a single arm study.

Actual start date of recruitment	07 November 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: 10

Worldwide total number of subjects	10
EEA total number of subjects	10

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)	5
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Three UK sites were opened to recruitment, three of these enrolled patients to the study. The first site opened to recruitment on 14/08/2012 and the first patient consent was on 07/11/2012. The study terminated on 26/11/12, after 13 patients had been enrolled.

Pre-assignment

Screening details:

15 patients were consented to the trial. 2 were found to be ineligible and 13 were enrolled into the trial. Of these 13, three did not start trial intervention (2 FLT PET scan failure; 1 Adverse Event)

Pre-assignment period milestones

Number of subjects started	15[1]
Intermediate milestone: Number of subjects	Confirmed Eligibilty: 13
Number of subjects completed	10

Pre-assignment subject non-completion reasons

Reason: Number of subjects	FLT PET Scan Failure: 2
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Ineligible: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 15 were consented and screened for the study. 2 patients were found to be ineligible during screening and 1 patient suffered an AE during screening and was withdrawn.

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	Interventional Arm

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.

Number of subjects in period 1	Interventional Arm
Started	10
Completed	8
Not completed	2
FLT PET Scan Failure	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

As per the Statistical Analysis Plan, only patients who received at least one dose of study drug are included in the analysis. Patients who were enrolled on the study, but did not start study treatment (N=3; withdrawal (1), day 1 scan failure (2)) are not included.

Reporting group values	Overall Trial	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 66.5 52 to 82	 -	
Gender categorical Units: Subjects			
Female	10	10	
Male	0	0	
Ethnicity Units: Subjects			
White	5	5	
Other White	5	5	
ER Status (Allred Score)			
Oestrogen Receptor Status			
Units: Subjects			
07	1	1	
08	9	9	
PgR Status (Allred score)			
Progesterone receptor status			
Units: Subjects			
03	1	1	
05	1	1	
06	1	1	
07	4	4	
08	3	3	
HER 2 Status			
Human epidermal growth factor receptor 2 status			
Units: Subjects			
IHC +++	4	4	
Negative	6	6	
Body Mass Index Units: kg/m2 median full range (min-max)	 26.3 20.5 to 35.3	 -	
Tumour Size			

Evaluated by Ultrasound			
Units: mm			
median	21		
full range (min-max)	15 to 48	-	

Subject analysis sets

Subject analysis set title	Intention to treat – evaluable for safety
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat – evaluable for safety	
Subject analysis set title	Per protocol analysis – evaluable for safety & efficacy
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol analysis – evaluable for safety & efficacy	

Reporting group values	Intention to treat – evaluable for safety	Per protocol analysis – evaluable for safety & efficacy	
Number of subjects	10	8	
Age categorical Units: Subjects			
Age continuous Units: years			
median	66.5	65.5	
full range (min-max)	52 to 82	52 to 79	
Gender categorical Units: Subjects			
Female	10	8	
Male	0	0	
Ethnicity Units: Subjects			
White	5	4	
Other White	5	4	
ER Status (Allred Score)			
Oestrogen Receptor Status			
Units: Subjects			
07	1	1	
08	9	7	
PgR Status (Allred score)			
Progesterone receptor status			
Units: Subjects			
03	1	1	
05	1	1	
06	1	1	
07	4	2	
08	3	3	
HER 2 Status			
Human epidermal growth factor receptor 2 status			
Units: Subjects			
IHC +++	4	4	

Negative	6	4	

Body Mass Index			
Units: kg/m2			
median	26.3	26.3	
full range (min-max)	20.5 to 35.3	20.6 to 35.7	
Tumour Size			
Evaluated by Ultrasound			
Units: mm			
median	21	21	
full range (min-max)	15 to 48	17 to 48	

End points

End points reporting groups

Reporting group title	Interventional Arm
Reporting group description: -	
Subject analysis set title	Intention to treat – evaluable for safety
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat – evaluable for safety	
Subject analysis set title	Per protocol analysis – evaluable for safety & efficacy
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol analysis – evaluable for safety & efficacy	

Primary: Changes in FLT uptake - SUV

End point title	Changes in FLT uptake - SUV[1]
End point description:	
End point type	Primary
End point timeframe: Changes in FLT uptake between Day 1 and Day 14 FLT-PET scan	

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	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: percent				
number (confidence interval 95%)	50 (22 to 78)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes in FLT uptake - SUVmax

End point title	Changes in FLT uptake - SUVmax[2]
End point description:	
End point type	Primary
End point timeframe: Changes in FLT uptake between Day 1 and Day 14 FLT-PET scan	

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	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: percent				
number (confidence interval 95%)	75 (41 to 93)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes in FLT uptake - Ki

End point title	Changes in FLT uptake - Ki[3]

End point description:

End point type	Primary

End point timeframe:

Changes in FLT uptake between Day 1 and Day 14 FLT-PET scan

Notes:

[3] - 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	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: percent				
number (confidence interval 95%)	71 (36 to 92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels - Oestradiol

End point title	Circulating Steroid Hormone Levels - Oestradiol

End point description:

To assess the pharmacodynamic profile of Irusostat

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[4]			
Units: ng/dL				
median (full range (min-max))				
Day 1	9.5 (4 to 19)			
Day 7	8.5 (3 to 31)			
Day 14	7 (3 to 28)			
Safety Follow-Up	5 (3 to 12)			

Notes:

[4] - Results for Safety Follow-up only include 5 patients

Attachments (see zip file)	Oestradiol Chart.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels - Oestrone

End point title	Circulating Steroid Hormone Levels - Oestrone

End point description:

To assess the pharmacodynamic profile of Irusostat

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[5]			
Units: ng/dL				
median (full range (min-max))				
Day 1	34 (22 to 62)			

Day 7	15.5 (9 to 36)			
Day 14	16 (9 to 41)			
Safety Follow-up	17 (9 to 23)			

Notes:

[5] - Results for Safety Follow-up only include 5 patients

Attachments (see zip file)	Oesterone.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels - Oestrone Sulphate

End point title	Circulating Steroid Hormone Levels - Oestrone Sulphate

End point description:

To assess the pharmacodynamic profile of Irusostat

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[6]			
Units: ng/dL				
median (full range (min-max))				
Day 1	376.5 (201 to 2001)			
Day 7	680 (148 to 1977)			
Day 14	664.5 (172 to 2240)			
Safety Follow-up	261 (222 to 1114)			

Notes:

[6] - Results for Day 7 only include 7 patients.
Results for Safety Follow-up only include 5 patients

Attachments (see zip file)	Oesterone Sulphate.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels – Dehydroepiandrosterone (DHEAS)

End point title	Circulating Steroid Hormone Levels – Dehydroepiandrosterone (DHEAS)

End point description:	
To assess the pharmacodynamic profile of Irusostat	
End point type	Secondary
End point timeframe:	
Samples were collected at Day 1, Day 7, Day 14 and Safety Follow	

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	6[7]			
Units: ng/dL				
median (full range (min-max))				
Day 1	102 (30 to 221)			
Day 7	101 (30 to 271)			
Day 14	160 (45 to 394)			
Safety Follow-Up	72 (31 to 379)			

Notes:

[7] - Results for Day 7, Day 14 and Safety Follow-up only include 5 patients.

Attachments (see zip file)	DHEAS.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels – Dehydroepiandrosterone (DHEA)

End point title	Circulating Steroid Hormone Levels – Dehydroepiandrosterone (DHEA)
End point description:	
To assess the pharmacodynamic profile of Irusostat	
End point type	Secondary
End point timeframe:	
Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up	

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[8]			
Units: ng/dL				
median (full range (min-max))				

Day 1	179 (49 to 279)			
Day 7	87 (40 to 216)			
Day 14	100 (75 to 169)			
Safety Follow-Up	68 (49 to 156)			

Notes:

[8] - Results for Day 1 only include 7 patients

Attachments (see zip file)	DHEA.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels - Testosterone

End point title	Circulating Steroid Hormone Levels - Testosterone

End point description:

To assess the pharmacodynamic profile of Irusostat

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	5[9]			
Units: ng/dL				
median (full range (min-max))				
Day 1	22 (9 to 37)			
Day 7	11 (9 to 19)			
Day 14	4 (4 to 22)			
Safety Follow-Up	8 (5 to 18)			

Notes:

[9] - Results from Day 14 only include 3 patients

Attachments (see zip file)	Testosterone.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels - Oesterone Sulphate / Oestrone ratio

End point title	Circulating Steroid Hormone Levels - Oesterone Sulphate / Oestrone ratio

End point description:

To assess the pharmacodynamic profile of Irusostat.
Ratio of Oesterone Sulphate / Oestrone results.

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[10]			
Units: ng/dL				
median (full range (min-max))				
Day 1	60.6 (14 to 177)			
Day 7	106.9 (19 to 253)			
Day 14	89.8 (34 to 262)			
Safety Follow-up	55.5 (20 to 371)			

Notes:

[10] - Results for Safety Follow Up only include 5 patients

Attachments (see zip file)	Oesterone Sulphate to Oesterone Ratio.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels - DHEAS / DHEA Ratio

End point title	Circulating Steroid Hormone Levels - DHEAS / DHEA Ratio

End point description:

To assess the pharmacodynamic profile of Irusostat.
Ratio of the DHEAS / DHEA results.

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/dL				
median (full range (min-max))				
Day 1	0.62 (0.5 to 0.9)			
Day 7	0.88 (0.7 to 2.6)			
Day 14	1.67 (0.5 to 3.5)			
Safety Follow-up	1.01 (0.5 to 4.3)			

Attachments (see zip file)	DHEAS to DHEA Ratio.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Steroid Hormone Levels – Androstenedione

End point title	Circulating Steroid Hormone Levels – Androstenedione

End point description:

To assess the pharmacodynamic profile of Irusostat

End point type	Secondary

End point timeframe:

Samples were collected at Day 1, Day 7, Day 14 and Safety Follow-up

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[11]			
Units: ng/dL				
median (full range (min-max))				
Day 1	55 (42 to 120)			
Day 7	38 (16 to 61)			
Day 14	48 (7 to 97)			
Safety Follow-up	47 (21 to 81)			

Notes:

[11] - Results for Day 1 only include 7 patients
Results for Safety Follow-up only include 5 patients

Attachments (see zip file)	Androstenedione.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Ki67 proliferation marker

End point title	Changes in Ki67 proliferation marker

End point description:

To assess the effect of Irosustat on breast tumour proliferation.

End point type	Other pre-specified

End point timeframe:

Ki67 was measured pre-treatment from patients diagnostic biopsies and post treatment from patients surgical samples.

End point values	Per protocol analysis – evaluable for safety & efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: percent				
median (full range (min-max))	52.3 (-19.7 to 76.4)			

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

Reporting groups

Reporting group title	Intention to Treat

Reporting group description:

All patients who had at least one dose of IMP

Serious adverse events	Intention to Treat		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 10 (10.00%)		
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	Intention to Treat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Vascular disorders			

Dizziness - Vascular subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Syncope subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Hot flush subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 4		
Electrocardiogram abnormal			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Glucose urine present subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Heart rate increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Platelet count increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Protein urine present subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dizziness - Nervous System subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Eye disorders			
Vision blurred subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Mouth ulceration			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Pruritis subjects affected / exposed occurrences (all) Skin discolouration subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 5 / 10 (50.00%) 7 1 / 10 (10.00%) 1 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal discomfort	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Spinal osteoarthritis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Nipple infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Viral pharyngitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypermagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
hypernatraemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2012	• End of trial definition amended to last patient, last data capture to bring it in line with latest guidance by the NRES. • Eligibility criteria: Decreased tumour size from ≥20mm to 15≥mm by either mammography, ultrasound examination or magnetic resonance imaging. This is the minimum tumour size that can be captured by a PET Scan for the purposes of this study. • Safety follow up visit amended to take place 7 days after the last administration of Irosustat instead of 30 days (in line with the half-life of Irosustat). • Updated SAE reporting process
05 November 2013	• Removal of STS analysis: As a result of a reduction in funding funds are no longer available to carry out STS Analysis. • Increase to blood sample volume collected during PET Scans: The total amount of venous blood taken during each FLT-PET scan and analysed for the relative contribution of FLT and its metabolite FLT-glucuronide was amended to include the amount of blood taken, but discarded, after the line has been flushed. • The screening period for all assessments was changed from 21 to 35 days to allow patients whose pathology results are delayed to be included in the study.
14 July 2014	• Duration of collection of AEs: Protocol amended so that any unresolved AEs at the time of the safety follow up visit that are considered to be related to the IMP can be followed up and recorded in the database until resolution or until termination of the study. Any new AEs that occur after the safety follow up visit and that are considered to be related to the IMP should also be recorded in the database and followed up until resolution or the termination of the study. • Removal of requirement to fast prior to scan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Defining response as decreases of ≥20% in SUV and ≥30% in Ki, we observed responses in 1 (12.5% (95%CI 2-47%, p=0.001)) and 3 (43% (95%CI 16-75%, p=<0.001) patients respectively.

Notes: