Clinical trial results:
The use of Peroxisome Proliferator Activator Receptor Agonists in the management of Androgen Independent Prostate Cancer

Summary

EudraCT number	2006-001398-44
Trial protocol	GB
Global end of trial date	24 November 2015

Results information

Result version number	v1 (current)
This version publication date	10 December 2016
First version publication date	10 December 2016

Trial information

Trial identification

Sponsor protocol code	PR 2006-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Dr Jonathan Shamash, Centre for Experimental Cancer Medicine, Charterhouse Square, London, EC1M 6BQ, +44 2078828493, bci-ppar@qmul.ac.uk
Scientific contact	Dr Jonathan Shamash, Centre for Experimental Cancer Medicine, Charterhouse Square, London, EC1M 6BQ, +44 02078828493, bci-ppar@qmul.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is PSA doubling time.

The secondary objectives are to find PSA response, symptomatic progression, restoration of androgen sensitivity, quality of life (using the EORTC QLQ-C30 and EORTC QLQ-PR25 quality of life assessments) and time to progression.

Protection of trial subjects:

Side effects were closely monitored during and after the study. Patients were required to attend regular clinic appointments whilst they were on study medication and adverse events were recorded. The patient information sheet included details on expected adverse events for patients to look out for and also detailed that unexpected events may occur. The Trial Management Group for the trial was in place throughout to closely assess the side effects of the drugs on a regular basis to make sure there were no excess risks to patients. On-site monitoring was performed throughout the study to provide real time review of source data to allow for early detection of signals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	0
From 65 to 84 years	44
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

From 1/2/2007, 49 patients out of an intended 67 were recruited by two hospitals within the UK only. Trial was terminated early in November 2015 due to slow recruitment.

Pre-assignment

Screening details:

Inclusion criteria allowed patients with androgen independent prostate cancer defined as rising PSA in the presence of MAB who were asymptomatic (ECOG 0-2).

Pre-assignment period milestones

Number of subjects started	49
Number of subjects completed	49

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	Overall trial

Arm description:

Single arm: Rosiglitazone/Pioglitazone followed by addition of fenofibrate, followed by addition of calcitriol.

Arm type	Experimental
Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	EU/1/00/150/011-015
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

45 mg once daily, orally

Investigational medicinal product name	Fenofibrate
Investigational medicinal product code	PL 00512/0391
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

267mg daily

Investigational medicinal product name	Calcitriol
Investigational medicinal product code	PL00031/0123
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

500 mcg daily

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

Dosage and administration details:

4mg BD for a minimum of 6 weeks orally

Number of subjects in period 1	Overall trial
Started	49
Rosiglitazone cohort	31 [1]
Pioglitazone cohort	18 [2]
Completed	47
Not completed	2
Consent withdrawn by subject	1
Protocol deviation	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Pioglitazone replaced the drug Rosiglitazone after recruiting 31 patients. Two patients were excluded from analysis. 18 patients were recruited to Pioglitazone. Therefor two cohorts of patients.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Pioglitazone replaced the drug Rosiglitazone after recruiting 31 patients. Two patients were excluded from analysis. 18 patients were recruited to Pioglitazone. Therefor two cohorts of patients.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Single arm: Rosiglitazone/Pioglitazone followed by addition of fenofibrate, followed by addition of calcitriol.	

Reporting group values	Overall trial	Total	
Number of subjects	49	49	
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			
median	75		
inter-quartile range (Q1-Q3)	70 to 82	-	
Gender categorical			
All subjects were male.			
Units: Subjects			
Female	0	0	
Male	49	49	
Gleason score Units: Subjects			
<7	5	5	
>=7	33	33	
missing	11	11	
Lower urinary tract symptoms Units: Subjects			
Yes	7	7	
No	39	39	
Missing	3	3	
Cardian history Units: Subjects			
Yes	10	10	
No	35	35	
Missing	4	4	
Respiratory Units: Subjects			
Yes	4	4	

No	42	42	
Missing	3	3	
Diagnosis method Units: Subjects			
Biopsy	38	38	
TURP	4	4	
Other	2	2	
Missing	5	5	
Has a TURP been performed? Units: Subjects			
Yes	8	8	
No	33	33	
Missing	8	8	
Clinical T category (1997) Units: Subjects			
T0	1	1	
T1	1	1	
T2	4	4	
T3	15	15	
T4	7	7	
TX	5	5	
Missing	16	16	
Prior radical prostechtomy Units: Subjects			
Yes	1	1	
No	43	43	
Missing	5	5	
Prior radical RT Units: Subjects			
Yes	10	10	
No	34	34	
Missing	5	5	
Metastases at study entry Units: Subjects			
Yes	15	15	
No	25	25	
Missing	9	9	
Metastases at diagnosis Units: Subjects			
Yes	15	15	
No	23	23	
Mising	11	11	
GnRH analogues? Units: Subjects			
Yes	34	34	
No	2	2	
Missing	13	13	
Maximum androgen blockage Units: Subjects			
Yes	41	41	
No	1	1	

Missing	7	7	
Bilateral orchidectomy Units: Subjects			
Yes	1	1	
No	7	7	
Missing	41	41	

Subject analysis sets

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

All consented patients took part in observational (pre-treatment) phase and/or received any medication

Reporting group values	Overall trial		
Number of subjects	47		
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			
median	75		
inter-quartile range (Q1-Q3)	70 to 82		
Gender categorical			
All subjects were male.			
Units: Subjects			
Female	0		
Male	47		
Gleason score Units: Subjects			
<7	5		
>=7	33		
missing	9		
Lower urinary tract symptoms Units: Subjects			
Yes	7		
No	39		
Missing	1		
Cardian history Units: Subjects			
Yes	10		
No	35		

Missing	2		
Respiratory Units: Subjects			
Yes	4		
No	42		
Missing	1		
Diagnosis method Units: Subjects			
Biopsy	38		
TURP	4		
Other	2		
Missing	3		
Has a TURP been performed? Units: Subjects			
Yes	8		
No	33		
Missing	6		
Clinical T category (1997) Units: Subjects			
T0	1		
T1	1		
T2	4		
T3	15		
T4	7		
TX	5		
Missing	14		
Prior radical prostechtomy Units: Subjects			
Yes	1		
No	43		
Missing	3		
Prior radical RT Units: Subjects			
Yes	10		
No	34		
Missing	3		
Metastases at study entry Units: Subjects			
Yes	15		
No	25		
Missing	7		
Metastases at diagnosis Units: Subjects			
Yes	15		
No	23		
Mising	9		
GnRH analogues? Units: Subjects			
Yes	34		
No	2		
Missing	11		

Maximum androgen blockage Units: Subjects			
Yes	41		
No	1		
Missing	5		
Bilateral orchidectomy Units: Subjects			
Yes	1		
No	7		
Missing	39		

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Single arm: Rosiglitazone/Pioglitazone followed by addition of fenofibrate, followed by addition of calcitriol.

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

All consented patients took part in observational (pre-treatment) phase and/or received any medication

Primary: PSA doubling time

End point title	PSA doubling time

End point description:

Time to PSA progression is defined as the time from start of treatment to when PSA progression is initially seen. PSA progression is defined by the PCWG2 criteria:

- Decline from baseline: Time from start of therapy to first PSA increase that is ≥25% and ≥2ng/mL above the nadir, and which is confirmed by a 2nd value 3 or more weeks later.
- No decline from baseline: PSA progression ≥25% and ≥2ng/mL after 12 weeks.

End point type	Primary

End point timeframe:

baseline to disease progression (PSA progression)

End point values	Overall trial	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	47		
Units: week				
median (inter-quartile range (Q1-Q3))	35 (17.5 to 144.1)	35 (17.5 to 144.1)		

Statistical analyses

Statistical analysis title	Wilcoxon sign rank sum test

Statistical analysis description:

Wilcoxon sign rank sum test comparing PSADT during the monitoring phase and treatment phases for the same patients.

Comparison groups	Overall trial v Overall trial
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.001
Method	Wilcoxon sign rank sum test

Notes:

[1] - Subject in this analysis is 47. Wilcoxon sign rank sum test compares PSADT between monitoring phase and treatment phases for the same patients.

Secondary: Restoration of androgen sensitivity

End point title	Restoration of androgen sensitivity

End point description:

PSA levels down from end of trial - after reintroduction of bicalutamide

End point type	Secondary

End point timeframe:

From end of trial - after reintroduction of bicalutamide

End point values	Overall trial			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: Number	2			

Statistical analyses

No statistical analyses for this end point

Secondary: PSA response

End point title	PSA response

End point description:

At least 50% reduction is PSA

End point type	Secondary

End point timeframe:

From start of treatment to progression/end of trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Number	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic progression

End point title	Symptomatic progression

End point description:

If patients had noted pain or a new symptom

End point type	Secondary

End point timeframe:

From start of treatment to progression

End point values	Overall trial	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	47		
Units: Number	8	8		

Statistical analyses

Statistical analysis title	Proportion
Comparison groups	Overall trial v Overall trial
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Proportion with CI
Parameter estimate	Proportion
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0764
upper limit	0.3081

Notes:

[2] - The symptomatic proportion is base on 47 patients.

Secondary: Time to progression

End point title	Time to progression

End point description:

End point type	Secondary

End point timeframe:

From study entry to progression/end of study

End point values	Overall trial	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	47		
Units: Weeks				
median (inter-quartile range (Q1-Q3))	23.7 (18 to 37)	23.7 (18 to 37)		

Attachments (see zip file)	K-M for Time to Progression/Kaplam Miere for TTP.docx

Statistical analyses

Statistical analysis title	K-M curve and Log-rank test

Statistical analysis description:

Log-rank test for the difference in progression free survival between patients who received Rosiglitazone and who received Pioglitazone.

Comparison groups	Overall trial v Overall trial
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0053 [4]
Method	Logrank

Notes:

[3] - Pioglitazone replaced the drug Rosiglitazone and hence this analysis. This analysis is based on 47 patients: Rosiglitazone (29) and Pioglitazone (18).
[4] - P-value from the Log-rank test.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From trial consent to 30 days after last dose of IMP.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	overall trial
Reporting group description: all patients that took part in the trial	

Serious adverse events	overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 47 (23.40%)		
number of deaths (all causes)	32		
number of deaths resulting from adverse events			
Surgical and medical procedures			
Aortic valve replacement			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Pancreatitis			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hydronephrosis			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 47 (100.00%)		
Investigations			

Weight gain subjects affected / exposed occurrences (all)	16 / 47 (34.04%) 25		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all)	 6 / 47 (12.77%) 7 7 / 47 (14.89%) 9 9 / 47 (19.15%) 11		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 36 / 47 (76.60%) 105 24 / 47 (51.06%) 45 32 / 47 (68.09%) 65		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Flatulence	 18 / 47 (38.30%) 38 9 / 47 (19.15%) 13		

subjects affected / exposed	11 / 47 (23.40%)		
occurrences (all)	20		
Nausea			
subjects affected / exposed	14 / 47 (29.79%)		
occurrences (all)	20		
Vomiting			
subjects affected / exposed	9 / 47 (19.15%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 47 (25.53%)		
occurrences (all)	28		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	7 / 47 (14.89%)		
occurrences (all)	13		
Urticaria			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Infections and infestations			
Stomatitis			
subjects affected / exposed	43 / 47 (91.49%)		
occurrences (all)	213		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	17 / 47 (36.17%)		
occurrences (all)	26		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2008	Reduction of minimum entry age to 16 years. Clarification of SUSAR reporting requirements.
24 September 2009	Introduction of weekly calcitriol monitoring
19 April 2011	Addition of Pioglitazone following withdrawal of Avandia.
23 November 2011	Updates to PIS following a Drug Safety Notification from MHRA for Pioglitazone.
29 May 2012	Update to Sponsor name due to institutional mergers.
24 January 2013	Inclusion criteria amended to allow pain in patients with previous chemotherapy if this is controlled with simple analgesics or codeine phosphate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported