



## Clinical trial results:

### A Cancer Research UK Phase I/II Open Label Study to Evaluate the Safety, Endocrine Effects and Anti-tumour Activity of Abiraterone Acetate (CB7630) in Patients with Oestrogen (ER) or Androgen Receptor (AR) Positive Advanced or Metastatic Breast Carcinoma.

#### Summary

EudraCT number	2007-003240-30
Trial protocol	GB
Global end of trial date	04 June 2016

#### Results information

Result version number	v1 (current)
This version publication date	17 February 2017
First version publication date	17 February 2017

#### Trial information

##### Trial identification

Sponsor protocol code	CR9304-21
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00755885
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Cancer Research UK
Sponsor organisation address	407 St John Street, London, United Kingdom, EC1V 4AD
Public contact	Centre for Drug Development, Cancer Research UK, +44 02072420200, regquery@cancer.org.uk
Scientific contact	Centre for Drug Development, Cancer Research UK, +44 02072420200, regquery@cancer.org.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	30 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2016
Global end of trial reached?	Yes
Global end of trial date	04 June 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this trial in post-menopausal women with ER+ or AR+ advanced or metastatic breast cancer were:

Phase I

1. To determine and establish the safety profile and tolerability of abiraterone acetate administered orally continuously in a once-daily regimen.
2. To recommend a trial dose for the Phase II evaluation.

Phase II

1. To evaluate the clinical benefit of abiraterone acetate at 24 weeks (i.e. after six cycles of treatment).
2. To further determine the safety profile and tolerability of abiraterone acetate administered orally continuously in a once-daily regimen.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2008
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: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	52
From 65 to 84 years	22
85 years and over	3

## Subject disposition

### Recruitment

Recruitment details:

For the overall trial participants were enrolled from 05 November 2008 to 30 May 2014 in seven clinical study centres in the UK. Study participants for the Phase I part of the trial were only enrolled at two of the seven clinical study centres whereas participants for the Phase II part were enrolled across all seven clinical study centres.

### Pre-assignment

Screening details:

Post-menopausal females with histologically/cytologically proven advanced/metastatic breast cancer with either ER+ (any AR status) or ER- (AR+) disease confirmed by immunohistochemistry. Patients had to have received previous treatment in the adjuvant or metastatic setting, have a WHO performance status of 0-2 and life expectancy of  $\geq 3$  months.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Phase I

Arm description:

Phase I dose escalation part of the trial to evaluate the safety profile of abiraterone and identify a recommended dose for Phase II investigation. Incremental dose steps of 100% from the starting dose of 250 mg, 500 mg, 1000 mg and 2000 mg were studied.

Arm type	Experimental
Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	CB7630
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone acetate was taken orally 1 hour before breakfast once daily in a continuous 28-day cycle for all patients participating in the trial.

At the start of the trial, abiraterone acetate was supplied as a simple formulation of capsules containing 250 mg of abiraterone acetate encapsulated in a gelatin capsule. Following a change in manufacturing in 2010 (Protocol Amendment 05), abiraterone acetate was supplied as tablets composed of 250 mg of abiraterone acetate and non-active ingredients (excipients).

All the Phase I patients commenced treatment with the capsule formulation, with only five patients receiving both formulations. All Phase II patients received the tablet formulation.

<b>Arm title</b>	Phase II
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Arm description:

Phase II part of the trial was a Gehan two-stage study design to evaluate the clinical benefit of abiraterone acetate in the two cohorts of patients ER+ (any AR status) and ER- (AR+) disease. The starting dose for Phase II evaluation was to be established from the Phase I part of the trial, or if the maximum tolerated dose (MTD) of abiraterone acetate was not reached during the Phase I part of the trial, a daily dose of 1000 mg abiraterone acetate was to be used for further evaluation.

Arm type	Experimental
Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	CB7630
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

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**Dosage and administration details:**

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At the start of the trial, abiraterone acetate was supplied as a simple formulation of capsules containing 250 mg of abiraterone acetate encapsulated in a gelatin capsule. Following a change in manufacturing in 2010 (Protocol Amendment 05), abiraterone acetate was supplied as tablets composed of 250 mg of abiraterone acetate and non-active ingredients (excipients).

All the Phase I patients commenced treatment with the capsule formulation, with only five patients receiving both formulations. All Phase II patients received the tablet formulation.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Phase I	Phase II
Started	25	50
Completed	25	50

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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: Only the safety population (i.e. enrolled patients who received abiraterone acetate) have been included (n=75). Two enrolled patients were withdrawn prior to the start of administration of abiraterone acetate (one patient in the Phase I part due to an AE of hydronephrosis and one patient in the Phase II part due to evidence of disease progression).

## Baseline characteristics

### Reporting groups

Reporting group title	Phase I
Reporting group description: Phase I dose escalation part of the trial to evaluate the safety profile of abiraterone and identify a recommended dose for Phase II investigation. Incremental dose steps of 100% from the starting dose of 250 mg, 500 mg, 1000 mg and 2000 mg were studied.	
Reporting group title	Phase II
Reporting group description: Phase II part of the trial was a Gehan two-stage study design to evaluate the clinical benefit of abiraterone acetate in the two cohorts of patients ER+ (any AR status) and ER- (AR+) disease. The starting dose for Phase II evaluation was to be established from the Phase I part of the trial, or if the maximum tolerated dose (MTD) of abiraterone acetate was not reached during the Phase I part of the trial, a daily dose of 1000 mg abiraterone acetate was to be used for further evaluation.	

Reporting group values	Phase I	Phase II	Total
Number of subjects	25	50	75
Age categorical Units: Subjects			
Adults (18-64 years)	19	32	51
From 65-84 years	6	15	21
85 years and over	0	3	3
Gender categorical Units: Subjects			
Female	25	50	75
Male	0	0	0
ER/AR disease type			
Patient's intra-tumoural ER and AR expression (ER+ [any AR status] and ER-[AR+]) disease type.			
Units: Subjects			
ER+ (any AR status)	23	26	49
ER-(AR+)	2	24	26

### Subject analysis sets

Subject analysis set title	Overall Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients for the overall trial who received at least one dose of abiraterone acetate.	
Subject analysis set title	Phase II Response Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients in the Phase II part of the study who were evaluable for tumour response (i.e. patients who had received at least two cycles of abiraterone acetate and had not missed more than 14 days of abiraterone treatment in one cycle).	
Subject analysis set title	Phase I Pharmacokinetic Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All enrolled and eligible patients who received at least one cycle of abiraterone acetate at doses ranging from 250 mg to 2000 mg and provided pre- and post-dose pharmacokinetic plasma samples.	
Subject analysis set title	Endocrine Profile Population

Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All enrolled eligible patients in the Phase I and II parts of the trial who received abiraterone acetate and provided pre- and post-treatment blood samples.

Reporting group values	Overall Safety Population	Phase II Response Population	Phase I Pharmacokinetic Population
Number of subjects	75	40	23
Age categorical			
Units: Subjects			
Adults (18-64 years)	51	27	17
From 65-84 years	21	11	6
85 years and over	3	2	0
Gender categorical			
Units: Subjects			
Female	75	40	23
Male	0	0	0
ER/AR disease type			
Patient's intra-tumoural ER and AR expression (ER+ [any AR status] and ER-[AR+]) disease type.			
Units: Subjects			
ER+ (any AR status)	49	22	21
ER-(AR+)	26	18	2

Reporting group values	Endocrine Profile Population		
Number of subjects	69		
Age categorical			
Units: Subjects			
Adults (18-64 years)	48		
From 65-84 years	18		
85 years and over	3		
Gender categorical			
Units: Subjects			
Female	69		
Male	0		
ER/AR disease type			
Patient's intra-tumoural ER and AR expression (ER+ [any AR status] and ER-[AR+]) disease type.			
Units: Subjects			
ER+ (any AR status)	48		
ER-(AR+)	21		

## End points

### End points reporting groups

Reporting group title	Phase I
Reporting group description: Phase I dose escalation part of the trial to evaluate the safety profile of abiraterone and identify a recommended dose for Phase II investigation. Incremental dose steps of 100% from the starting dose of 250 mg, 500 mg, 1000 mg and 2000 mg were studied.	
Reporting group title	Phase II
Reporting group description: Phase II part of the trial was a Gehan two-stage study design to evaluate the clinical benefit of abiraterone acetate in the two cohorts of patients ER+ (any AR status) and ER- (AR+) disease. The starting dose for Phase II evaluation was to be established from the Phase I part of the trial, or if the maximum tolerated dose (MTD) of abiraterone acetate was not reached during the Phase I part of the trial, a daily dose of 1000 mg abiraterone acetate was to be used for further evaluation.	
Subject analysis set title	Overall Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients for the overall trial who received at least one dose of abiraterone acetate.	
Subject analysis set title	Phase II Response Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients in the Phase II part of the study who were evaluable for tumour response (i.e. patients who had received at least two cycles of abiraterone acetate and had not missed more than 14 days of abiraterone treatment in one cycle).	
Subject analysis set title	Phase I Pharmacokinetic Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All enrolled and eligible patients who received at least one cycle of abiraterone acetate at doses ranging from 250 mg to 2000 mg and provided pre- and post-dose pharmacokinetic plasma samples.	
Subject analysis set title	Endocrine Profile Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All enrolled eligible patients in the Phase I and II parts of the trial who received abiraterone acetate and provided pre- and post-treatment blood samples.	

### Primary: Safety

End point title	Safety <sup>[1]</sup>
End point description: The causality and severity grading of each adverse event (AE) to abiraterone acetate, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. AEs with a causality of possibly, probably or almost certainly related were considered to indicate relatedness. Dose limiting toxicity (DLT) was defined as almost certainly or probably related to abiraterone acetate and occurring during Cycle 1: a) Absolute neutrophil count $<0.5 \times 10^9/L$ for more than 7 days or $<0.5 \times 10^9/L$ with neutropenic fever/sepsis. b) Platelet count $<25 \times 10^9/L$ . c) Non-haematological $\geq$ Grade 3 toxicity excluding Grade 3 fatigue, nausea, vomiting, diarrhoea, myalgia, arthralgia (in patients who had not received prophylactic/therapeutic measures). d) Toxicities due to elevated mineralocorticoids if concurrent therapeutic measures failed to suppress the ACTH feedback loop. e) Grade 4 hypertension. f) Any toxicity deemed by the Sponsor/Investigators as a DLT.	
End point type	Primary
End point timeframe: From patient consent to 28 days post last dose of abiraterone acetate.	



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: All safety data were presented in a descriptive fashion, with AEs presented by CTCAE adverse event term by worst grade observed.

End point values	Phase I	Phase II	Overall Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	50	75	
Units: Number of AEs				
All AEs	251	551	802	
Related AEs	56	185	241	
DLTs	0	0	0	

## Statistical analyses

No statistical analyses for this end point

## Primary: Clinical benefit rate at 24 weeks

End point title	Clinical benefit rate at 24 weeks <sup>[2]</sup>
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End point description:

For the Phase II part of the trial only, the determination of the number of patients with an objective response (partial response, complete response or stable disease) after six cycles of abiraterone acetate (i.e. at least 24 weeks) according to RECIST (Version 1.0).

End point type	Primary
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End point timeframe:

From the start of abiraterone acetate daily dosing until at least 24 weeks (i.e. six cycles of treatment).

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: Proportion of Phase II patients with an objective response after six cycles presented as per the study protocol.

End point values	Phase II Response Population			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: Number of patients				
Objective response (ER+ [any AR])	4			
No objective response (ER+ [any AR])	18			
Objective response (ER- [AR+])	2			
No objective response (ER- [AR+])	16			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tumour response

End point title	Tumour response
End point description:	
<p>All patients who met eligibility criteria, received at least two cycles of abiraterone acetate (56 days continuous daily dosing), had a baseline assessment of disease and at least one repeat disease assessment were evaluable for response. A patient in Phase I must have received at least 21 of the 28 days of dosing in the first cycle and patients in the Phase II part of the trial were considered to be evaluable for response as long as they had not missed &gt;14 days of treatment in one cycle. Any response, complete response (CR) or partial response (PR), or stable disease (SD), in any of the patients was defined by Response Evaluation Criteria in Solid Tumours (RECIST).</p> <p>For a status of CR or PR, changes in tumour measurements had to be confirmed by repeat measurements performed no less than 4 weeks after the response criteria were met. For a status of SD, follow-up measurements had to meet SD criteria at least once and at least 8 weeks after study treatment had started.</p>	
End point type	Secondary
End point timeframe:	
From baseline assessment and then after every two cycles.	

End point values	Phase I	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: Number of patients				
Complete Response	0	0		
Partial Response	1	0		
Stable Disease	5	25		
Progressive Disease	12	15		
Early Progression	1	2		
Not Evaluable	6	8		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abiraterone acetate pharmacokinetic profile

End point title	Abiraterone acetate pharmacokinetic profile
End point description:	
<p>Performed in patients enrolled in the Phase I dose escalation part of the trial, who received at least one cycle of abiraterone acetate and provided pre- and post-dose pharmacokinetic plasma samples. Pharmacokinetic parameters estimated included: time of maximum observed concentration (Tmax), maximum concentration (Cmax), terminal half-life of the drug (HL Lambda z), area under the concentration v time curve from time of dosing to the last measureable concentration (AUClast), area under the concentration v time curve from time of dosing extrapolated to infinity (AUCINF obs), total body clearance (Cl F obs) and volume of distribution (Vz F obs).</p>	
End point type	Secondary
End point timeframe:	
Pre-treatment (within one week prior to dosing), Cycle 1 Day 1 through to Cycle 2 Day 1 and off-study.	

End point values	Phase I Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number of patients				
Dose level 250 mg	6			
Dose Level 500 mg	6			
Dose Level 1000 mg	5			
Dose Level 2000 mg	6			

<b>Attachments (see zip file)</b>	CR9304-21 Mean Pharmacokinetic Parameters for Abiraterone
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Two-year survival

End point title	Two-year survival <sup>[3]</sup>
End point description: Two-year survival was measured for all eligible patients in the Phase II part of the trial who received abiraterone acetate (measured from the date of their first dose of abiraterone acetate).	
End point type	Secondary
End point timeframe: For the Phase II patients only, two-year survival measured from Cycle 1 Day 1 of abiraterone acetate administration.	
Notes: [3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The evaluation of two-year survival was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.	

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: months				
median (full range (min-max))				
ER+ (any AR) patients	7.8 (1.3 to 19.8)			
ER- (AR+) patients	8.2 (0.8 to 21.6)			
All Phase II patients	7.9 (0.8 to 21.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Endocrine impact of abiraterone acetate

End point title	Endocrine impact of abiraterone acetate
End point description:	
All eligible patients in the Phase I and II parts of the trial who received abiraterone acetate and provided pre- and post-treatment blood samples were examined to assess the endocrine impact of abiraterone acetate on the pituitary-adrenal-gonad endocrine axis to determine the relationship with dose (Phase I) and tumour response rates (Phase II). Blood samples were taken to measure the endocrine levels of the following: oestrone, oestradiol [oestradiol-17 beta, E2], 17-OH-progesterone, testosterone, cortisol, corticosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA-sulphate, lutenising hormone, follicle stimulating hormone, and sex hormone binding globulin.	
End point type	Secondary
End point timeframe:	
Blood samples were taken at baseline, Cycle 1 and throughout the trial until the time of disease progression.	

End point values	Endocrine Profile Population			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Number of Patients				
Phase I patients	25			
Phase II patients	44			

<b>Attachments (see zip file)</b>	Abiraterone Endocrine Profile CSR extract
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From patient consent to 28 days post last dose of abiraterone acetate.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	3.0
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### Reporting groups

Reporting group title	Phase I
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Reporting group description:

Phase I dose escalation part of the trial to evaluate the safety profile of abiraterone and identify a recommended dose for Phase II investigation. Incremental dose steps of 100% from the starting dose of 250 mg, 500 mg, 1000 mg and 2000 mg were studied.

Reporting group title	Phase II
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Reporting group description:

Phase II part of the trial was a Gehan two-stage study design to evaluate the clinical benefit of abiraterone acetate in the two cohorts of patients ER+ (any AR status) and ER- (AR+) disease. The starting dose for Phase II evaluation was to be established from the Phase I part of the trial, or if the maximum tolerated dose (MTD) of abiraterone acetate was not reached during the Phase I part of the trial, a daily dose of 1000 mg abiraterone acetate was to be used for further evaluation.

Reporting group title	Overall Trial
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Reporting group description:

All patients treated with abiraterone acetate in both parts of the trial (Phase I and II).

Serious adverse events	Phase I	Phase II	Overall Trial
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 25 (44.00%)	21 / 50 (42.00%)	32 / 75 (42.67%)
number of deaths (all causes)	1	4	5
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Thrombosis/thrombus/embolism			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General disorders and administration site conditions			
Oedema limb			
subjects affected / exposed	0 / 25 (0.00%)	3 / 50 (6.00%)	3 / 75 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	0 / 25 (0.00%)	2 / 50 (4.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 25 (0.00%)	2 / 50 (4.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death - disease progression			
subjects affected / exposed	1 / 25 (4.00%)	2 / 50 (4.00%)	3 / 75 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 3
Immune system disorders			
Allergy - other specify			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 25 (12.00%)	4 / 50 (8.00%)	7 / 75 (9.33%)
occurrences causally related to treatment / all	0 / 3	1 / 4	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Hypotension			
subjects affected / exposed	2 / 25 (8.00%)	0 / 50 (0.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 50 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood anxiety			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurology - other specify			
subjects affected / exposed	1 / 25 (4.00%)	0 / 50 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 25 (4.00%)	0 / 50 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - neuralgia/peripheral			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	4 / 50 (8.00%)	5 / 75 (6.67%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distension			
subjects affected / exposed	0 / 25 (0.00%)	2 / 50 (4.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dysphagia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - abdomen not otherwise specified			
subjects affected / exposed	1 / 25 (4.00%)	1 / 50 (2.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - peritoneum			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Obstruction genitourinary - ureter			
subjects affected / exposed	1 / 25 (4.00%)	0 / 50 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 25 (4.00%)	0 / 50 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Endocrine - other specify			



subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal - extremity lower			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - back			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - bone			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - chest wall			
subjects affected / exposed	1 / 25 (4.00%)	1 / 50 (2.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection - other specify			
subjects affected / exposed	2 / 25 (8.00%)	4 / 50 (8.00%)	6 / 75 (8.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection normal ANC - catheter-related			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	2 / 25 (8.00%)	5 / 50 (10.00%)	7 / 75 (9.33%)
occurrences causally related to treatment / all	2 / 2	4 / 5	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bilirubin</b>			
subjects affected / exposed	0 / 25 (0.00%)	1 / 50 (2.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Phase I	Phase II	Overall Trial
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	49 / 50 (98.00%)	74 / 75 (98.67%)
<b>Investigations</b>			
Weight gain			
subjects affected / exposed	0 / 25 (0.00%)	5 / 50 (10.00%)	5 / 75 (6.67%)
occurrences (all)	0	6	6
Weight loss			
subjects affected / exposed	4 / 25 (16.00%)	0 / 50 (0.00%)	4 / 75 (5.33%)
occurrences (all)	4	0	4
<b>Cardiac disorders</b>			
Hypertension			
subjects affected / exposed	1 / 25 (4.00%)	4 / 50 (8.00%)	5 / 75 (6.67%)
occurrences (all)	1	5	6
Hypotension			
subjects affected / exposed	2 / 25 (8.00%)	1 / 50 (2.00%)	3 / 75 (4.00%)
occurrences (all)	2	1	3
<b>Nervous system disorders</b>			
Dizziness			
subjects affected / exposed	6 / 25 (24.00%)	7 / 50 (14.00%)	13 / 75 (17.33%)
occurrences (all)	6	7	13
Neurology - other specify			
subjects affected / exposed	2 / 25 (8.00%)	0 / 50 (0.00%)	2 / 75 (2.67%)
occurrences (all)	2	0	2
Neuropathy sensory			

subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	6 / 50 (12.00%) 11	11 / 75 (14.67%) 16
Pain headache subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 5	3 / 50 (6.00%) 3	6 / 75 (8.00%) 8
Pain neuralgia/peripheral nerve subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 50 (6.00%) 3	3 / 75 (4.00%) 3
Blood and lymphatic system disorders Haemoglobin subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	5 / 50 (10.00%) 12	8 / 75 (10.67%) 15
Neutrophils subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 50 (4.00%) 2	4 / 75 (5.33%) 4
General disorders and administration site conditions Constitutional symptoms - other subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 50 (6.00%) 3	3 / 75 (4.00%) 3
Fatigue subjects affected / exposed occurrences (all)	8 / 25 (32.00%) 9	28 / 50 (56.00%) 35	36 / 75 (48.00%) 44
Fever subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	5 / 50 (10.00%) 6	6 / 75 (8.00%) 8
Oedema limb subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6	11 / 50 (22.00%) 16	17 / 75 (22.67%) 22
Oedema head and neck subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 50 (2.00%) 1	3 / 75 (4.00%) 3
Pain chest/thorax not otherwise specified subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 50 (4.00%) 2	4 / 75 (5.33%) 4
Pain - other specify			

subjects affected / exposed	2 / 25 (8.00%)	4 / 50 (8.00%)	6 / 75 (8.00%)
occurrences (all)	2	4	6
Flu-like syndrome			
subjects affected / exposed	3 / 25 (12.00%)	3 / 50 (6.00%)	6 / 75 (8.00%)
occurrences (all)	3	3	6
Oedema trunk/genital			
subjects affected / exposed	2 / 25 (8.00%)	0 / 50 (0.00%)	2 / 75 (2.67%)
occurrences (all)	2	0	2
Hypothermia			
subjects affected / exposed	0 / 25 (0.00%)	3 / 50 (6.00%)	3 / 75 (4.00%)
occurrences (all)	0	6	6
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	4 / 25 (16.00%)	9 / 50 (18.00%)	13 / 75 (17.33%)
occurrences (all)	4	11	15
Constipation			
subjects affected / exposed	7 / 25 (28.00%)	15 / 50 (30.00%)	22 / 75 (29.33%)
occurrences (all)	8	18	26
Diarrhoea			
subjects affected / exposed	4 / 25 (16.00%)	8 / 50 (16.00%)	12 / 75 (16.00%)
occurrences (all)	5	12	17
Dry mouth			
subjects affected / exposed	3 / 25 (12.00%)	6 / 50 (12.00%)	9 / 75 (12.00%)
occurrences (all)	3	6	9
Heartburn			
subjects affected / exposed	2 / 25 (8.00%)	6 / 50 (12.00%)	8 / 75 (10.67%)
occurrences (all)	2	9	11
Nausea			
subjects affected / exposed	11 / 25 (44.00%)	18 / 50 (36.00%)	29 / 75 (38.67%)
occurrences (all)	16	23	39
Oesophagitis			
subjects affected / exposed	2 / 25 (8.00%)	1 / 50 (2.00%)	3 / 75 (4.00%)
occurrences (all)	2	1	3
Vomiting			
subjects affected / exposed	6 / 25 (24.00%)	14 / 50 (28.00%)	20 / 75 (26.67%)
occurrences (all)	7	23	30

Pain abdomen not otherwise specified subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 7	3 / 50 (6.00%) 3	9 / 75 (12.00%) 10
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 6  8 / 25 (32.00%) 8	12 / 50 (24.00%) 14  11 / 50 (22.00%) 13	17 / 75 (22.67%) 20  19 / 75 (25.33%) 21
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)  Mood anxiety subjects affected / exposed occurrences (all)  Mood depression subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3  1 / 25 (4.00%) 1  0 / 25 (0.00%) 0	7 / 50 (14.00%) 8  3 / 50 (6.00%) 4  3 / 50 (6.00%) 3	10 / 75 (13.33%) 11  4 / 75 (5.33%) 5  3 / 75 (4.00%) 3
Endocrine disorders Hot flashes subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	9 / 50 (18.00%) 9	14 / 75 (18.67%) 14
Musculoskeletal and connective tissue disorders Pain back subjects affected / exposed occurrences (all)  Pain bone subjects affected / exposed occurrences (all)  Pain chest wall subjects affected / exposed occurrences (all)  Pain extremity limb	6 / 25 (24.00%) 7  7 / 25 (28.00%) 9  2 / 25 (8.00%) 2	7 / 50 (14.00%) 7  3 / 50 (6.00%) 5  4 / 50 (8.00%) 5	13 / 75 (17.33%) 14  10 / 75 (13.33%) 14  6 / 75 (8.00%) 7

subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	9 / 50 (18.00%) 10	13 / 75 (17.33%) 14
Pain joint subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7	9 / 50 (18.00%) 12	16 / 75 (21.33%) 19
Pain muscle subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	6 / 50 (12.00%) 7	6 / 75 (8.00%) 7
Infections and infestations Infection- other specify subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 8	11 / 50 (22.00%) 17	17 / 75 (22.67%) 25
Metabolism and nutrition disorders ALT subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	4 / 50 (8.00%) 4	5 / 75 (6.67%) 5
AST subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	4 / 50 (8.00%) 4	6 / 75 (8.00%) 6
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	4 / 50 (8.00%) 9	4 / 75 (5.33%) 9
Hypokalaemia subjects affected / exposed occurrences (all)	16 / 25 (64.00%) 33	17 / 50 (34.00%) 31	33 / 75 (44.00%) 64
Metabolic/Lab - other specify subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	4 / 50 (8.00%) 7	5 / 75 (6.67%) 8

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2008	Changes to the inclusion/exclusion criteria, including the amendment to allow ER-patients to be enrolled into the trial and revision of the lower diastolic pressure limit for eligibility and DLT assessment. Addition of anti-tumour activity as a secondary objective in the Phase I part of the trial and removal of immunohistochemistry as a primary assay. DLT criteria amended to include Grade 4 hypertension. Several non-substantial changes made to rectify text omissions and provide further clarifications of the trial schedule.
30 October 2009	Additional section added to the protocol to describe the management of abnormal liver function tests (LFTs), including the addition of extra blood sampling following observation of Grade 2 abnormal LFTs. Clarification of the dose reduction and delay requirements plus the addition of non-hepatic toxicity relating to the management of hypokalaemia. Time frame and details added to clarify when measures should be taken in the event potassium supplements fail to maintain serum potassium levels.
11 February 2010	Addition and clarification of the mandated use of prophylactic hydrocortisone during abiraterone acetate administration to manage potential endocrine toxicities, along with clarifications relating to the management of hypokalaemia and hypertension. Further clarification of the protocol sections relating to the observation and management of abnormal LFTs. Change to allow the use of ECHO scans as well as MUGA scans to monitor cardiac function.
16 August 2010	Addition of four new study centres. Clarification of inclusion/exclusion criteria including previous lines of treatment for malignant disease, persistent Grade 2 toxicities, requirement of an ACTH stimulation test (Phase II) and allowing chest CT to be used as part of the screening evaluations. Additional guidance provided on the long term management of hypertension.
19 August 2010	Change of formulation from capsules to tablets as continued capsule manufacture was not considered suitable for large scale manufacture.
12 September 2011	Amendment to the definition of post-menopausal to clarify the accepted scenarios for confirming patient eligibility. Updates to the pharmacodynamic parameters and sampling time points.
01 May 2013	Additional guidance regarding the handling of abiraterone acetate and the risk to pregnant women or women who may become pregnant.
15 January 2014	Survival objective and endpoint amended from 'overall survival' to 'two-year survival' after treatment, along with clarification of the associated change to the definition of End of Trial.
15 April 2014	Change in manufacturer responsible for packaging, labelling, storage, and dispatch to sites.

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.

None reported.

Notes: