# 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 |

**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 ≥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 |
| **Arm title** | 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.

| | |
|---|---|
| **Arm title** | Phase II |

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 |
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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.

| **Number of subjects in period 1[1]** | Phase I | Phase II |
|---|---|---|
| Started | 25 | 50 |
| Completed | 25 | 50 |

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<br>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<br>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 |
|---|---|

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<br>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<br>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<br>Units: Subjects | | | |
| Adults (18-64 years) | 48 | | |
| From 65-84 years | 18 | | |
| 85 years and over | 3 | | |
| Gender categorical<br>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[1] |
|---|---|

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 x 10^9/L for more than 7 days or <0.5 x 10^9/L with neutropenic fever/sepsis.
b) Platelet count <25 x 10^9/L.
c) Non-haematological ≥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[2] |
|---|---|

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 |
|---|---|

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:

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 >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).
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.

| 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:

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 Lamda 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).

| 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 | | | |

| Attachments (see zip file) | CR9304-21 Mean Pharmacokinetc Parameters for Abiraterone |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Two-year survival

| End point title | Two-year survival[3] |
|---|---|

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 pateints | 25 | | | |
| Phase II patients | 44 | | | |

| **Attachments (see zip file)** | Abiraterone Endocrine Profile CSR extract |
|---|---|

## 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 3.0 |

### 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 title | Overall Trial |

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 gentiourinary - 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 |
| Bilirubin | | | |
| 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 %

| **Non-serious adverse events** | 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%) |
| Investigations | | | |
| 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 |
| Cardiac disorders | | | |
| 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 |
| Nervous system disorders | | | |
| 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 | 5 / 25 (20.00%) | 6 / 50 (12.00%) | 11 / 75 (14.67%) |
| occurrences (all) | 5 | 11 | 16 |
| Pain headache | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 3 / 50 (6.00%) | 6 / 75 (8.00%) |
| occurrences (all) | 5 | 3 | 8 |
| Pain neuralgia/peripheral nerve | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 3 / 50 (6.00%) | 3 / 75 (4.00%) |
| occurrences (all) | 0 | 3 | 3 |
| Blood and lymphatic system disorders | | | |
| Haemoglobin | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 5 / 50 (10.00%) | 8 / 75 (10.67%) |
| occurrences (all) | 3 | 12 | 15 |
| Neutrophils | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 2 / 50 (4.00%) | 4 / 75 (5.33%) |
| occurrences (all) | 2 | 2 | 4 |
| General disorders and administration site conditions | | | |
| Constitutional symptoms - other | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 3 / 50 (6.00%) | 3 / 75 (4.00%) |
| occurrences (all) | 0 | 3 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 8 / 25 (32.00%) | 28 / 50 (56.00%) | 36 / 75 (48.00%) |
| occurrences (all) | 9 | 35 | 44 |
| Fever | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 5 / 50 (10.00%) | 6 / 75 (8.00%) |
| occurrences (all) | 2 | 6 | 8 |
| Oedema limb | | | |
| subjects affected / exposed | 6 / 25 (24.00%) | 11 / 50 (22.00%) | 17 / 75 (22.67%) |
| occurrences (all) | 6 | 16 | 22 |
| Oedema head and neck | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 50 (2.00%) | 3 / 75 (4.00%) |
| occurrences (all) | 2 | 1 | 3 |
| Pain chest/thorax not otherwise specified | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 2 / 50 (4.00%) | 4 / 75 (5.33%) |
| occurrences (all) | 2 | 2 | 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 | 6 / 25 (24.00%) | 3 / 50 (6.00%) | 9 / 75 (12.00%) |
| occurrences (all) | 7 | 3 | 10 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 25 (20.00%) | 12 / 50 (24.00%) | 17 / 75 (22.67%) |
| occurrences (all) | 6 | 14 | 20 |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 25 (32.00%) | 11 / 50 (22.00%) | 19 / 75 (25.33%) |
| occurrences (all) | 8 | 13 | 21 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 7 / 50 (14.00%) | 10 / 75 (13.33%) |
| occurrences (all) | 3 | 8 | 11 |
| Mood anxiety | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 3 / 50 (6.00%) | 4 / 75 (5.33%) |
| occurrences (all) | 1 | 4 | 5 |
| Mood depression | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 3 / 50 (6.00%) | 3 / 75 (4.00%) |
| occurrences (all) | 0 | 3 | 3 |
| Endocrine disorders | | | |
| Hot flashes | | | |
| subjects affected / exposed | 5 / 25 (20.00%) | 9 / 50 (18.00%) | 14 / 75 (18.67%) |
| occurrences (all) | 5 | 9 | 14 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain back | | | |
| subjects affected / exposed | 6 / 25 (24.00%) | 7 / 50 (14.00%) | 13 / 75 (17.33%) |
| occurrences (all) | 7 | 7 | 14 |
| Pain bone | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 3 / 50 (6.00%) | 10 / 75 (13.33%) |
| occurrences (all) | 9 | 5 | 14 |
| Pain chest wall | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 4 / 50 (8.00%) | 6 / 75 (8.00%) |
| occurrences (all) | 2 | 5 | 7 |
| Pain extremity limb | | | |

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