# Clinical trial results:
# Phase II trial of Linsitinib (anti-IGF-1R/IR) in patients with relapsed and/or refractory Ewing Sarcoma

## Summary

| | |
|---|---|
| EudraCT number | 2012-000616-28 |
| Trial protocol | GB IT NL |
| Global end of trial date | 03 October 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 28 June 2017 |
| First version publication date | 28 June 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | OCTO_038 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02546544 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Oxford |
| Sponsor organisation address | Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LE |
| Public contact | Joint Research Office, University of Oxford, ctrg@admin.ox.ac.uk |
| Scientific contact | Joint Research Office, University of Oxford, ctrg@admin.ox.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 | 06 December 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 October 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To determine the effect of the trial drug (linsitinib) on the patient's tumours in terms of changes in biomarker and PET scans.
To establish the safety of the trial drug (linsitinib) in Ewing sarcoma at the dose and treatment schedule being used in the trial.

Protection of trial subjects:

The trial was reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC) or equivalent for the non-UK countries (IRB etc.). Approval to conduct the study was obtained from the relevant Competent Authority in each participating country prior to initiating the study. In the UK the study was conducted under a Medicines and Healthcare products Regulatory Agency (MHRA) Clinical Trial Authorisation (CTA). The sponsor and investigators ensured that the trial was run in compliance with the European Clinical Trials Regulations, the Principles of Good Clinical Practice (GCP) and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.
The trial design formally built in early stopping rules for treatment futility and/or toxicity to reduce the number of patients receiving an ineffective and/or toxic treatment.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 25 April 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Germany: 2 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 16 |

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) | 16 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from April 2014 until March 2016 at specialist cancer hospitals across Europe

### Pre-assignment

Screening details:

29 patients were assessed for eligibility. 13 patients were excluded: seven did not meet the inclusion criteria, five declined to participate and one passed away prior to starting screening.

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Linsitinib |

Arm description:

Linsitinib

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Linsitinib |
| Investigational medicinal product code | |
| Other name | ASP7487, OSI-906 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Linsitinib is to be taken orally once a day on days 1-3, 8-10 and 15-17 on a 21 day cycle. The starting dose is 600 mg.

| **Number of subjects in period 1** | Linsitinib |
|---|---|
| Started | 16 |
| Received allocated intervention | 16 |
| Completed | 0 |
| Not completed | 16 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 1 |
| Disease Progression | 14 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Linsitinib |
| Reporting group description:<br>Linsitinib | |

| Reporting group values | Linsitinib | Total | |
|---|---|---|---|
| Number of subjects | 16 | 16 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 16 | 16 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 13 | 13 | |
| Region of Enrollment<br>Units: Subjects | | | |
| United Kingdom | 8 | 8 | |
| Italy | 4 | 4 | |
| Netherlands | 2 | 2 | |
| Germany | 2 | 2 | |
| WHO performance status<br>Units: Subjects | | | |
| WHO PS 0 | 5 | 5 | |
| WHO PS 1 | 7 | 7 | |
| WHO PS 2 | 4 | 4 | |
| Histology<br>Units: Subjects | | | |
| Ewing Sarcoma | 16 | 16 | |
| Primary site<br>Units: Subjects | | | |
| Chest wall | 4 | 4 | |
| Extra-osseous site | 2 | 2 | |
| Lower extremity | 3 | 3 | |
| Pelvis | 5 | 5 | |
| Spine | 1 | 1 | |
| Upper extremity | 1 | 1 | |
| Disease stage at screening | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Metastatic | 16 | 16 | |
| Number of lines of previous treatment<br>Units: Subjects | | | |
| Second line | 1 | 1 | |
| Third line | 1 | 1 | |
| > third line | 14 | 14 | |
| Prior radiotherapy<br>Units: Subjects | | | |
| Yes | 13 | 13 | |
| No | 3 | 3 | |
| Prior chemotherapy<br>Units: Subjects | | | |
| Yes | 16 | 16 | |
| Prior surgery<br>Units: Subjects | | | |
| Yes | 14 | 14 | |
| No | 2 | 2 | |
| Site of Metastases - Bone<br>Units: Subjects | | | |
| Yes | 3 | 3 | |
| No | 13 | 13 | |
| Sites of Metastases - Lung<br>Units: Subjects | | | |
| Yes | 11 | 11 | |
| No | 5 | 5 | |
| Site of Metastases - Bone, Other<br>Units: Subjects | | | |
| Yes | 8 | 8 | |
| No | 8 | 8 | |
| Time since most recent relapse/progression (days)<br>Units: days | | | |
| median | 18 | | |
| inter-quartile range (Q1-Q3) | 12 to 39 | - | |

## End points

### End points reporting groups

| Reporting group title | Linsitinib |
|---|---|
| Reporting group description: Linsitinib | |

### Primary: To determine the pharmacodynamic effect of Linsitinib in the tumour (FDG uptake (SUV) responses in ES tumours using functional imaging 18FDG-PET-CT) evaluated using PERCIST.

| End point title | To determine the pharmacodynamic effect of Linsitinib in the tumour (FDG uptake (SUV) responses in ES tumours using functional imaging 18FDG-PET-CT) evaluated using PERCIST.[1] |
|---|---|
| End point description: Pharmacodynamic FDG uptake (SUV) responses in ES tumours using functional imaging 18FDG-PET-CT and repeat post treatment biopsies to establish biomarker responses in tumour biopsies. Response measured by PERCIST using SULpeak. | |
| End point type | Primary |
| End point timeframe: Pre- and Post- dose responses following 1 cycle (21 days) of treatment | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a co primary endpoint. The proportion of patients with a partial or complete metabolic response according to PERCIST was used. The analysis was done using a Bayesian model. 1/16 patients satisfied this endpoint and thus the treatment was deemed to be ineffective according to the model.

### Statistical analyses

No statistical analyses for this end point

### Primary: To evaluate the safety of Linsitinib

| End point title | To evaluate the safety of Linsitinib[2] |
|---|---|
| End point description: A patient is defined as having a toxic event if they experienced at least one grade 3 adverse event (CTCAE v4.0 grade) | |
| End point type | Primary |
| End point timeframe: Following 6 cycles of treatment (up to 6 months) | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a co primary endpoint. The proportion of patients with at least one adverse event of grade 3 or higher was used. The analysis was done using a Bayesian model. 5/16 patients satisfied this endpoint and thus the treatment was deemed to have a greater than acceptable toxicity level according

to the model.

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: subjects | | | | |
| Experienced a toxic event | 5 | | | |
| Did not experienced a toxic event | 11 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical outcome (PFS)

| End point title | Clinical outcome (PFS) |
|---|---|

End point description:

To determine the clinical outcome through assessment of
- Progression free survival; where length of survival is defined in whole days as the time from entry into the study until Ewing sarcoma progression or death from any cause.

Note that the upper end the of confidence interval was undefined.

| End point type | Secondary |
|---|---|

End point timeframe:

Duration of study (up to 18 months)

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.28 (0.66 to 999) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Radiological Response as Measured by EORTC 1.0

| End point title | Radiological Response as Measured by EORTC 1.0 |
|---|---|

End point description:

Radiological Response as Measured by EORTC 1.0. This methodology used SUVmax to measure change in glucose uptake in the tumour. Evaluated on site reported data.

| End point type | Secondary |
|---|---|

End point timeframe:

Measured cycle 1 day 15

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical outcome (DSS)

| End point title | Clinical outcome (DSS) |
|---|---|

End point description:

To determine the clinical outcome through assessment of
- Disease specific survival; where length of survival is defined in whole days as the time from entry into the study until death from Ewing sarcoma.

Note that the upper end the of confidence interval was undefined.

| End point type | Secondary |
|---|---|

End point timeframe:

Duration of study (up to 18 months)

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.13 (2.56 to 999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Radiological response measured by RECIST

| End point title | Radiological response measured by RECIST |
|---|---|

End point description:

Radiological response measured using RECIST version 1.1

| End point type | Secondary |
|---|---|

End point timeframe:

cycle 1 day 15

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: subjects | | | | |
| Stable disease | 7 | | | |
| Progressive disease | 7 | | | |
| No paired scan | 2 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|
| End point description: | |
| Plasma concentrations of linsitinib | |
| End point type | Secondary |
| End point timeframe: | |
| Screening | |

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 1 (1 to 1) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|
| End point description: | |
| Plasma concentrations of linsitinib | |
| End point type | Secondary |

End point timeframe:

Cycle 1 Day 1

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 4790 (286 to 7538) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|

End point description:

Plasma concentrations of linsitinib

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 day 15

| End point values | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 2163 (1090 to 3206) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|

End point description:

Plasma concentrations of linsitinib

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 day 17

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 4977 (144 to 9628) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|

End point description:

Plasma concentrations of linsitinib

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 2 day 3

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 3409 (1534 to 5284) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|

| | |
|---|---|
| End point description:<br>Plasma concentrations of linsitinib | |
| End point type | Secondary |
| End point timeframe:<br>Cycle 3 day 1 | |

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 6791 (849 to 8478) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)**

| | |
|---|---|
| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
| End point description:<br>Plasma concentrations of linsitinib | |
| End point type | Secondary |
| End point timeframe:<br>Cycle 3 day 3 | |

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 1964 (417 to 14080) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)**

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|

End point description:

Plasma concentrations of linsitinib

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 4 day 1

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 3591 (3591 to 3591) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib)**

| End point title | Pharmacokinetics assays of following linsitinib treatment (Plasma concentrations of linsitinib) |
|---|---|

End point description:

Plasma concentrations of linsitinib

| End point type | Secondary |
|---|---|

End point timeframe:

End of treatment visit

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Concentration of Linsitinib (ng/ml) | | | | |
| median (full range (min-max)) | 1 (1 to 1432) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Radiological response measured by RECIST**

| End point title | Radiological response measured by RECIST |
|---|---|

End point description:

Radiological response measured using RECIST version 1.1

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 3 day 3

| **End point values** | Linsitinib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Patients | | | | |
| Stable disease | 2 | | | |
| Progressive disease | 4 | | | |
| No paired scan | 10 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Adverse events were collected from baseline until 28 days post treatment. | |
| Assessment type | Non-systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |
| **Reporting groups** | |
| Reporting group title | Linsitinib |
| Reporting group description: | |
| Linsitinib | |

| Serious adverse events | Linsitinib | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | | |
| number of deaths (all causes) | 13 | | |
| number of deaths resulting from adverse events | 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Linsitinib | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 16 (93.75%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | | |
| occurrences (all) | 4 | | |
| Chest pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 3 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Electrocardiogram QT prolonged | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | | |
| occurrences (all) | 11 | | |
| Lymphocyte count decreased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Haemoglobin decreased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Spinal cord injury | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 3 | | |
| Somnolence | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Constipation | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Diarrhoea | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Vomiting | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Back pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Flank pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Pharyngitis streptococcal | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Respiratory tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Decreased appetite | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | | |
| occurrences (all) | 3 | | |
| Hypokalaemia | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Hypomagnesaemia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 09 February 2014 | Changes to the protocol and PIS to reflect updated information in the Investigator Brochure for Linsitinib. |
| 24 September 2014 | Amendments to the protocol schedule of events for PET CT and biopsy. This was done to ensure repeat biopsies could be obtained in the event of progressive disease.<br>Submission of updated investigational medicinal product dossier. Submission of updated Investigator Brochure. |
| 09 April 2015 | Amend eligibility criteria.<br>Amend the protocol to say that all patients who discontinue study treatment in the event of >= grade 3 ECG QTc prolongation must be monitored by continuous ECG until resolution or stabilisation. This change was requested by a country level ethics board. |
| 23 November 2015 | Amend statistical design in protocol to reflect final SAP. Improvements to the design identified and implemented to reduce the type I and type II error rates increase the likelihood of stopping early in the event of a very effective, ineffective or toxic drug whilst using the same number of participants. |

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.

The trial was halted early due to a pre-planned stopping rule. This led to a small number of subjects to analyse.

Notes: