EU Clinical Trials Register

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:	
Linsitinib	

Reporting group values	Linsitinib	Total	
Number of subjects	16	16	
Age categorical			
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			
Units: Subjects			
Female	3	3	
Male	13	13	
Region of Enrollment			
Units: Subjects			
United Kingdom	8	8	
Italy	4	4	
Netherlands	2	2	
Germany	2	2	
WHO performance status			
Units: Subjects			
WHO PS 0	5	5	
WHO PS 1	7	7	
WHO PS 2	4	4	
Histology			
Units: Subjects			
Ewing Sarcoma	16	16	
Primary site			
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 Units: Subjects			
Second line	1	1	
Third line	1	1	
> third line	14	14	
Prior radiotherapy Units: Subjects			
Yes	13	13	
No	3	3	
Prior chemotherapy Units: Subjects			
Yes	16	16	
Prior surgery Units: Subjects			
Yes	14	14	
No	2	2	
Site of Metastases - Bone Units: Subjects			
Yes	3	3	
No	13	13	
Sites of Metastases - Lung Units: Subjects			
Yes	11	11	
No	5	5	
Site of Metastases - Bone, Other Units: Subjects			
Yes	8	8	
No	8	8	
Time since most recent relapse/progression (days) 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:
Plasma concentrations of linsitinib

End point type	Secondary

End point timeframe:
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:
Plasma concentrations of linsitinib

End point type	Secondary

End point timeframe:
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. Submission of updated investigational medicinal product dossier. Submission of updated Investigator Brochure.
09 April 2015	Amend eligibility criteria. 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: