Clinical trial results:
A Mechanistic Study Of Mifamurtide (MTP-PE) In Patients With Metastatic And/Or Recurrent Osteosarcoma

Summary

EudraCT number	2012-000615-84
Trial protocol	IT NL DE
Global end of trial date	09 December 2016

Results information

Result version number	v1 (current)
This version publication date	16 August 2017
First version publication date	16 August 2017

Trial information

Trial identification

Sponsor protocol code	OCTO_039

Additional study identifiers

ISRCTN number	ISRCTN46249783
ClinicalTrials.gov id (NCT number)	NCT02441309
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	19 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2016
Global end of trial reached?	Yes
Global end of trial date	09 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The principal research question is to identify markers of response to mifurmatide by looking at biological markers of immune response activation in tumour biopsies taken before and after 6 weeks of treatment. The pharmacodynamic readouts will be compared with radiological (CT scan) response measured by standard RECIST criteria.

Protection of trial subjects:

The Sponsor and Investigators ensured that the protocol was conducted 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 (2013) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive. The protocol, patient information sheet and consent form was reviewed and approved by an appropriately constituted, UK independent Research Ethics Committee (REC) or national equivalent. Approval to conduct the study was obtained from the relevant Competent Authority in each participating country prior to initiating the study.

The Investigators monitored each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Adverse event monitoring starts from the time the patient consents to the study until they complete the trial.

Background therapy:

There is currently no approved treatment other than surgery for metastatic or recurrent osteosarcoma refractory to chemotherapy. Patients deemed unresectable normally receive chemotherapy prior to attempted resection.

Evidence for comparator:

Mifamurtide is licensed for use in the adjuvant osteosarcoma setting, The addition of chemotherapy to surgery may improve response rates. This trial will investigate why some patients with osteosarcoma may respond better than others to mifamurtide given alone or in combination with ifosfamide. All participants will receive 36 weeks or more of mifamurtide.

Actual start date of recruitment	15 July 2015
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	Netherlands: 1
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	1
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment opened in October 2014 with the first patient being recruited on the 15th July 2015. The trial closed in June 2016 due to a poor recruitment rate.

Pre-assignment

Screening details:

18 Patients were assessed for eligibility. 10 patients were excluded, 4 did not meet the inclusion/exclusion criteria and 6 declined to participate.

Period 1

Period 1 title	Main study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Resectable Cohort

Arm description:

Patients who were deemed resectable at registration were placed in this group. They received Mifamurtide alone with the option to have surgeries at baseline and after 6 weeks (2 cycles) of treatment.

Arm type	Experimental
Investigational medicinal product name	Mifamurtide
Investigational medicinal product code	Mifamurtide
Other name	MEPACT
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weeks 1-12 (cycles 1-4): Mifamurtide 2 mg/m2, IV infusion, twice per week, with each infusion given at least 3 days apart, for 6 weeks.
Weeks 13-36 (cycles 5-12): Mifamurtide 2 mg/m2, IV infusion, once per week.

Arm title	Unresectable Control arm

Arm description:

Unresectable patients who were allocated to received mifamurtide after the primary endpoint timepoint (6 weeks or 2 cycles of treatment). Patients received Ifosfamide for 4 three weekly cycles. Patients received 12 3 weekly cycles of Mifamurtide starting after completing 2 cycles of Ifosfamide.

Arm type	Active comparator
Investigational medicinal product name	Mifamurtide
Investigational medicinal product code	Mifamurtide
Other name	MEPACT
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

weeks 7-18 (cycles 3-6): Mifamurtide 2 mg/m2, IV infusion, twice per week, with each infusion given at least 3 days apart, for 6 weeks.
weeks 19-42 (cycles 7-14): Mifamurtide 2 mg/m2, IV infusion, once per week.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	Ifosfamide
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Day 1 of each a 21 day cycle: Ifosfamide 12-15 g/m2 IV infusion infused over 4-5 days as per local practice. Repeated every 21 days for two cycles (3 weeks = 1 cycle). Ifosfamide administered as per local institutional practice, including concurrent dosing with mesna.

Arm title	Unresectable Experimental Arm

Arm description:

Unresectable patients allocated to this arm received 4 three weekly cycles of Ifosfamide and 12 three weekly cycles of Mifamurtide both starting at baseline.

Arm type	Experimental
Investigational medicinal product name	Mifamurtide
Investigational medicinal product code	Mifamurtide
Other name	MEPACT
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weeks 1-12 (cycles 1-4): Mifamurtide 2 mg/m2, IV infusion, twice per week, with each infusion given at least 3 days apart, for 6 weeks.
Weeks 13-36 (cycles 5-12): Mifamurtide 2 mg/m2, IV infusion, once per week.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	Ifosfamide
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Day 1 of each a 21 day cycle: Ifosfamide 12-15 g/m2 IV infusion infused over 4-5 days as per local practice. Repeated every 21 days for two cycles (3 weeks = 1 cycle). Ifosfamide administered as per local institutional practice, including concurrent dosing with mesna.

Number of subjects in period 1	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm
Started	3	2	3
6 week scan (primary endpoint)	1	1	2
Completed	0	0	0
Not completed	3	2	3
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	-	1	-
Lack of efficacy	2	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Main study

Reporting group description: -

Reporting group values	Main study	Total	
Number of subjects	8	8	
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)	1	1	
Adults (18-64 years)	7	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	24.5		
inter-quartile range (Q1-Q3)	20.2 to 34.5	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	7	7	
WHO Performance Status Units: Subjects			
WHO ps 0	6	6	
Who ps 1	2	2	
Histology/ Cytological type Units: Subjects			
Chondroblastic OS - 9181/3	1	1	
Osteoblastic OS - 9180/3	2	2	
Osteosarcoma NOS - 9180/3	5	5	
Primary Site Units: Subjects			
Axial	3	3	
Limb	5	5	
Disease stage at screening Units: Subjects			
Metastatic	8	8	
Prior Chemotherapy Units: Subjects			
Yes	2	2	
No	6	6	

Prior Radiotherapy Units: Subjects			
Yes	8	8	
Prior Surgery Units: Subjects			
Yes	8	8	
Tumour size at baseline (sum of longest diameters) Units: mm			
median	82		
inter-quartile range (Q1-Q3)	51 to 92	-	

End points

End points reporting groups

Reporting group title	Resectable Cohort

Reporting group description:

Patients who were deemed resectable at registration were placed in this group. They received Mifamurtide alone with the option to have surgeries at baseline and after 6 weeks (2 cycles) of treatment.

Reporting group title	Unresectable Control arm

Reporting group description:

Unresectable patients who were allocated to received mifamurtide after the primary endpoint timepoint (6 weeks or 2 cycles of treatment). Patients received Ifosfamide for 4 three weekly cycles. Patients received 12 3 weekly cycles of Mifamurtide starting after completing 2 cycles of Ifosfamide.

Reporting group title	Unresectable Experimental Arm

Reporting group description:

Unresectable patients allocated to this arm received 4 three weekly cycles of Ifosfamide and 12 three weekly cycles of Mifamurtide both starting at baseline.

Primary: Radiological Response Defined as Complete or Partial Response and Assessed Using RECIST Criteria

End point title	Radiological Response Defined as Complete or Partial Response and Assessed Using RECIST Criteria[1]

End point description:

Radiological response defined as complete or partial response and assessed using RECIST criteria

End point type	Primary

End point timeframe:

Change from Baseline to after 6 weeks 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: The trial halted early and thus no statistical analysis was completed.

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Stable disease	0	1	1	
Progressive disease	0	0	1	
Patient did not reach endpoint	1	1	1	
Patient progression prior to endpoint	2	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Biological Response Data Based on Pharmacodynamic Endpoints on Tumour Biopsy Material

End point title	Biological Response Data Based on Pharmacodynamic Endpoints on Tumour Biopsy Material[2]

End point description:

Biological response data based on pharmacodynamic endpoints on tumour biopsy material including macrophage
infiltration and innate immune activation.

End point type	Primary

End point timeframe:

Change from Baseline to after 6 weeks 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: This endpoint has not yet been completed.

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: Macrophage count				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[3] - Endpoint currently being analysed

[4] - Endpoint currently being analysed

[5] - Endpoint currently being analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Radiological Response Based on RECIST 1.1 (week 12)

End point title	Objective Radiological Response Based on RECIST 1.1 (week 12)

End point description:

Objective radiological response based on RECIST 1.1

End point type	Secondary

End point timeframe:

Change from Baseline to after 12 weeks of treatment

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Stable disease	0	1	1	
Progressive disease	0	0	0	
Patient did not reach endpoint	3	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Radiological Response Based on RECIST 1.1 (week 18)

End point title	Objective Radiological Response Based on RECIST 1.1 (week 18)

End point description:

Objective radiological response based on RECIST 1.1

End point type	Secondary

End point timeframe:

from Baseline to after 18 weeks of treatment

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Stable disease	0	1	0	
Progressive disease	0	0	1	
Patient did not reach endpoint	3	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Radiological Response Based on RECIST 1.1 (week 24)

End point title	Objective Radiological Response Based on RECIST 1.1 (week 24)

End point description:

Objective radiological response based on RECIST 1.1

End point type	Secondary

End point timeframe:

Change from Baseline to after 24 weeks of treatment

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Stable disease	0	1	0	
Progressive disease	0	0	0	
Patient did not reach endpoint	3	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Radiological Response Based on RECIST 1.1 (week 36)

End point title	Objective Radiological Response Based on RECIST 1.1 (week 36)

End point description:

Objective radiological response based on RECIST 1.1

End point type	Secondary

End point timeframe:

Change from Baseline to after 36 weeks of treatment

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Stable disease	0	0	0	
Progressive disease	0	1	0	
Patient did not reach endpoint	3	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory Abnormalities (Grade 3-4)

End point title	Laboratory Abnormalities (Grade 3-4)

End point description:

Laboratory abnormalities grade 3 and 4

End point type	Secondary

End point timeframe:

Up to 42 weeks

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Yes	0	0	0	
No	3	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Specific Overall Survival

End point title	Disease Specific Overall Survival

End point description:

The time from registration/randomisation to death due to the disease. Surviving patients and deaths due to other cause
will be censored at their last follow-up date. Patients lost to Follow-up without an event will be censored at the date of
their last consultation.

End point type	Secondary

End point timeframe:

Up to 42 weeks

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[6]	0[7]	0[8]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[6] - Trial Stopped early, endpoint not analysed

[7] - Trial Stopped early, endpoint not analysed

[8] - Trial Stopped early, endpoint not analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity (Graded According to the CTCAE Criteria)

End point title	Toxicity (Graded According to the CTCAE Criteria)

End point description:

Grade 3+ Toxicity measured and graded according to the CTCAE criteria

End point type	Secondary

End point timeframe:

Up to 42 weeks

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: subjects				
Experiences a grade 3+ adverse event	0	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival on Serial CT Scan

End point title	Progression Free Survival on Serial CT Scan

End point description:

Time from randomisation for deemed non-resectable groups, or time from registration for deemed resectable group to
first event, where an event is progression as (defined by RECIST criterion) or death due to any cause. Patients who
have not had an event will be censored at their last follow-up date. Patients lost to follow-up without an event will be
censored at the date of their last consultation.

End point type	Secondary

End point timeframe:

Up to 42 weeks

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	0[10]	0[11]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[9] - Trial Stopped early, endpoint not analysed

[10] - Trial Stopped early, endpoint not analysed

[11] - Trial Stopped early, endpoint not analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Radiological Response Based on RECIST 1.1 (end of treatment prior to week 6)

End point title	Objective Radiological Response Based on RECIST 1.1 (end of treatment prior to week 6)

End point description:

Objective radiological response based on RECIST 1.1

End point type	Secondary

End point timeframe:

Change from Baseline to end of treatment visit before week 6

End point values	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	0[12]	0[13]	
Units: Patients				
Stable disease	0			
Progressive disease	2			

Notes:

[12] - No patient had a end of treatment scan prior to week 6

[13] - No patient had a end of treatment scan prior to week 6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from baseline until discontinuation of all trial treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Resectable Cohort

Reporting group description:

Patients who were deemed resectable at registration were placed in this group. They received Mifamurtide alone with the option to have surgeries at baseline and after 6 weeks (2 cycles) of treatment.

Reporting group title	Unresectable Control arm

Reporting group description:

Unresectable patients who were allocated to received mifamurtide after the primary endpoint timepoint (6 weeks or 2 cycles of treatment). Patients received Ifosfamide for 4 three weekly cycles. Patients received 12 3 weekly cycles of Mifamurtide starting after completing 2 cycles of Ifosfamide.

Reporting group title	Unresectable Experimental Arm

Reporting group description:

Unresectable patients allocated to this arm received 4 three weekly cycles of Ifosfamide and 12 three weekly cycles of Mifamurtide both starting at baseline.

Serious adverse events	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	2 / 2 (100.00%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pseudomonas infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Resectable Cohort	Unresectable Control arm	Unresectable Experimental Arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 2 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	1 / 3 (33.33%)
occurrences (all)	1	4	1
Taste altered			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	1 / 3 (33.33%)
occurrences (all)	0	8	1
Fever			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Flu like symptoms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Shivering			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Vomiting			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Shortness of breath			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Muscle weakness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Central line infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infected toe			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	5	0
Pseudomonas infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2015	Amend the protocol inclusion/ exclusion criteria and the statistical considerations for the trial in order to optimise the trial's design. Also the addition of four new sites.
16 December 2015	Updated to allow for an alternative GFR renal function screening assessment technique and an alternative cardiological screening assessment technique.
27 July 2016	Early closure of recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported