Clinical trial results:
Study to investigate the therapeutic equivalence of OsvaRen® tablets and OsvaRen® granules

Summary

EudraCT number	2012-004178-24
Trial protocol	DE
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	RP-OSV_02D_Final-Study-Report-OsvarenNEW_Synopsis (RP-OSV_02D_Final-Study-Report-OsvarenNEW_§13-9-GCP-V-v01_FINAL_20160404-S.pdf)

Trial information

Trial identification

Sponsor protocol code	RP-OSV-02-D

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02027662
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fresenius Medical Care Deutschland GmbH
Sponsor organisation address	Else-Kroener-Straße 1 , Bad Homburg, Germany, 61352
Public contact	Clinical Research, Fresenius Medical Care Deutschland GmbH, 49 6172 609 5248, Manuela.Stauss-Grabo@fmc-ag.com
Scientific contact	Clinical Research, Fresenius Medical Care Deutschland GmbH, 49 6172 609 5248, Manuela.Stauss-Grabo@fmc-ag.com

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	18 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the therapeutic equivalence of OsvaRen® granules and tablets. Adult patients on chronic haemodialysis or haemodiafiltration treatment with a diagnosis of hyperphosphataemia were randomised to receive either the study drug (OsvaRen® granules) or the control drug (OsvaRen® tablets) for a period of 4 weeks following a three-week run-in phase. Thereafter, patients on study drug received the control drug and vice versa. The primary parameter to test this was the serum phosphate level at the end of each treatment period.

Protection of trial subjects:

Every reasonable precaution has been taken to protect the health and safety of subjects.

Background therapy:

Extracorporeal renal replacement therapy for end stage renal failure

Evidence for comparator: -	
Actual start date of recruitment	02 January 2014
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	Germany: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	19

From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Selection of eligible patients: Adults on three-times weekly chronic haemodialysis or haemodiafiltration treatment with a diagnosis of hyperphosphataemiawere included.

Pre-assignment

Screening details:

Eligible patients were adults on chronic haemodialysis or haemodiafiltration treatment with a diagnosis of hyperphosphataemia inluded according the defined inclusion criteria.

Pre-assignment period milestones

Number of subjects started	61
Number of subjects completed	61

Period 1

Period 1 title	Run-in-phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Run-in-phase: Baseline Population

Arm description:

The main purpose of the run-in phase was to ensure that the patient’s serum phosphate level was sufficiently stable under the anti-hyperphosphataemic treatment with OsvaRen® tablets in order to commence the actual study (constant lower than or equal to 1.00 mmol/L).

Arm type	Active comparator
Investigational medicinal product name	OsvaRen® tablets
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

12 DF dosage form per day

Number of subjects in period 1	Run-in-phase: Baseline Population
Started	61
Completed	58
Not completed	3
Phosphat levels too variable	2
Consent withdrawn by subject	1

Period 2	
Period 2 title	Treatment 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	OsvaRen® tablets

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	OsvaRen® tablets
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

12 DF dosage form per day

Arm title	OsvaRen® granules

Arm description: -

Arm type	Experimental
Investigational medicinal product name	OsvaRen® granules
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

12 DF dosage form per day

Number of subjects in period 2	OsvaRen® tablets	OsvaRen® granules
Started	29	29
Completed	29	26
Not completed	0	3
Adverse event, non-fatal	-	2
Taste intolerable	-	1

Period 3	
Period 3 title	Treatment 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	OsvaRen® granules

Arm description: -

Arm type	Experimental
Investigational medicinal product name	OsvaRen® granules
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

12 DF dosage form per day

Arm title	OsvaRen® tablets

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	OsvaRen® tablets
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

12 DF dosage form per day

Number of subjects in period 3	OsvaRen® granules	OsvaRen® tablets
Started	29	26
Completed	27	24
Not completed	2	2
Adverse event, serious fatal	-	1
Adverse event, non-fatal	1	1
Taste intolerable	1	-

Baseline characteristics

Reporting groups

Reporting group title	Run-in-phase

Reporting group description:

The main purpose of the 3 week run-in phase was to ensure that the patient's serum phosphate levels are constant lower than or equal to 1.00 mmol/L.

Reporting group values	Run-in-phase	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
Adults (18-80 years)	61	61	
Age continuous Units: years			
median	69.5		
full range (min-max)	33 to 80	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	17	17	
missing	1	1	
Ethnic group Units: Subjects			
Caucasian	60	60	
missing	1	1	
Height Units: cm			
arithmetic mean	173.0		
standard deviation	± 9.6	-	
Pre-Dialysis Weight Units: kg			
arithmetic mean	87.4		
standard deviation	± 20.1	-	
Post-Dialysis Weight Units: kg			
arithmetic mean	85.5		
standard deviation	± 19.9	-	
Body mass index BMI Units: kg/m2			
arithmetic mean	28.1		
standard deviation	± 6.8	-	

Subject analysis sets

Subject analysis set title	Safety Population (SP)
Subject analysis set type	Full analysis

Subject analysis set description:

SP: includes all subjects who were included in the study by giving informed consent

Subject analysis set title	Treatment (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT: includes all subjects who were randomized and for whom valid data is available for at least one post-baseline assessment of serum phosphorous.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

PP: includes all subjects who entered the study in accordance with both the inclusion / exclusion criteria without major protocol deviations, who were randomized and who finished the study in accordance with the study protocol

Reporting group values	Safety Population (SP)	Treatment (ITT)	Per Protocol (PP)
Number of subjects	61	55	26
Age categorical Units: Subjects			
Adults (18-80 years)	61	55	26
Age continuous Units: years			
median	69.5	70.0	72
full range (min-max)	33 to 80	33 to 80	33 to 79
Gender categorical Units: Subjects			
Female	17	13	3
Male	43	42	23
missing	1	0	0
Ethnic group Units: Subjects			
Caucasian	60	55	26
missing	1	0	0
Height Units: cm			
arithmetic mean	173.0	173.8	173.6
standard deviation	± 9.6	± 9.0	± 8.7
Pre-Dialysis Weight Units: kg			
arithmetic mean	87.4	88.1	86.5
standard deviation	± 20.1	± 19.5	± 16.8
Post-Dialysis Weight Units: kg			
arithmetic mean	85.5	86.1	84.3
standard deviation	± 19.9	± 19.2	± 16.5
Body mass index BMI Units: kg/m2			
arithmetic mean	28.7	28.6	28.3
standard deviation	± 6.8	± 6.5	± 7.0

End points

End points reporting groups

Reporting group title	Run-in-phase: Baseline Population

Reporting group description:

The main purpose of the run-in phase was to ensure that the patient's serum phosphate level was sufficiently stable under the anti-hyperphosphataemic treatment with OsvaRen® tablets in order to commence the actual study (constant lower than or equal to 1.00 mmol/L).

Reporting group title	OsvaRen® tablets
Reporting group description: -	
Reporting group title	OsvaRen® granules
Reporting group description: -	
Reporting group title	OsvaRen® granules
Reporting group description: -	
Reporting group title	OsvaRen® tablets
Reporting group description: -	
Subject analysis set title	Safety Population (SP)
Subject analysis set type	Full analysis

Subject analysis set description:

SP: includes all subjects who were included in the study by giving informed consent

Subject analysis set title	Treatment (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT: includes all subjects who were randomized and for whom valid data is available for at least one post-baseline assessment of serum phosphorous.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

PP: includes all subjects who entered the study in accordance with both the inclusion / exclusion criteria without major protocol deviations, who were randomized and who finished the study in accordance with the study protocol

Primary: Serum phosphate ratio tablets/granules after 4 weeks treatment

End point title	Serum phosphate ratio tablets/granules after 4 weeks treatment

End point description:

The aim of primary analysis for this study is to show equivalence in serum phosphate concentrations after 4 weeks of treatment with OsvaRen® Tablets and OsvaRen® Granulate respectively.

End point type	Primary

End point timeframe:

Phosphate ratio tablets/granules after 4 weeks treatment phase

End point values	Treatment (ITT)	Per Protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	26		
Units: Phophate ratio				
log mean (confidence interval 95%)	0.97 (0.91 to 1.05)	0.94 (0.86 to 1.02)		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Per Protocol (PP) v Treatment (ITT)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.25

Secondary: Serum phosphate ratio tablets/granules after 2 weeks of each treatment phase

End point title	Serum phosphate ratio tablets/granules after 2 weeks of each treatment phase
End point description:	
Absolute serum phosphate ratio tablets/granules and 95% CI after 2 weeks of each treatment phase	
End point type	Secondary
End point timeframe:	
Phosphate ratio tablets/granules after 2 weeks of each treatment phase	

End point values	Treatment (ITT)	Per Protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	26		
Units: Phosphate ratio				
log mean (confidence interval 95%)	0.96 (0.89 to 1.02)	0.98 (0.88 to 1.10)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Treatment (ITT) v Per Protocol (PP)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.25

Secondary: Number of patients with serum phosphate levels <1.76 mmol/l (ITT)

End point title	Number of patients with serum phosphate levels <1.76 mmol/l (ITT)

End point description:

Number of patients with a serum phosphate level ≤1.76 mmol/L after 4 weeks treatment (subject analysis set: ITT)

End point type	Secondary

End point timeframe:

Comparing quoted end point after 4 weeks of treatment with test drug (OsvaRen granules) and comparator drug (OsvaRen tablets)

End point values	OsvaRen® tablets	OsvaRen® granules	OsvaRen® granules	OsvaRen® tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	27	26	24
Units: numbers	19	15	18	20

Statistical analyses

Statistical analysis title	Secondary endpoint

Statistical analysis description:

Number of patients with serum phosphate levels <1.76 mmol/l (ITT).
For secondary analysis of the proportion of patients with serum phosphate < 1.76 mmol/l Prescott's test will be employed.

Comparison groups	OsvaRen® tablets v OsvaRen® granules v OsvaRen® granules v OsvaRen® tablets

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Prescott’s test
Parameter estimate	Proportion
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.25

Secondary: Number of patients with serum phosphate levels <1.76 mmol/l (PP)

End point title	Number of patients with serum phosphate levels <1.76 mmol/l (PP)

End point description:

Number of patients with a serum phosphate level ≤1.76 mmol/L after 4 weeks treatment (subject analysis set: PP)

End point type	Secondary

End point timeframe:

Comparing quoted end point after 4 weeks of treatment with test drug (OsvaRen granules) and comparator drug (OsvaRen tablets)

End point values	OsvaRen® tablets	OsvaRen® granules	OsvaRen® granules	OsvaRen® tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	14	14
Units: numbers	9	7	10	11

Statistical analyses

Statistical analysis title	Secondary endpoint

Statistical analysis description:

Number of patients with serum phosphate levels <1.76 mmol/l (PP).
For secondary analysis of the proportion of patients with serum phosphate < 1.76 mmol/l Prescott’s test will be employed.

Comparison groups	OsvaRen® tablets v OsvaRen® granules v OsvaRen® granules v OsvaRen® tablets

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Prescott’s test
Parameter estimate	Proportion
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.25

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The documentation of AEs started after the patient signed the informed consent and continued until end of study.

Adverse event reporting additional description:

All AEs occurring during the study were documented by the investigator on the AE page of the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

All recruited patients were exposed to the study drug and were included in the safety population (N=61).

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 61 (19.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Colonoscopy			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Angiogram			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt thrombosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt occlusion			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head trauma with contusion			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 61 (85.25%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Neoplasm skin			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Haematoma			

subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	8 / 61 (13.11%)		
occurrences (all)	18		
Surgical and medical procedures			
Fracture reduction			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
General disorders and administration site conditions			
Contusion	Additional description: SOCS: Gastrointestinal disorders; Injury, poisoning and procedural complications		
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Device connection issue			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Impaired healing			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Injection site bruising			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Instillation site pain			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Thrombosis in device			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	3		
Ulcer			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Vessel puncture site haematoma			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Application site haematoma	Additional description: Abdominal pain upper Diarrhoea		
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	12		
Cough			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	5		
Dysphonia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Epistaxis			

subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2		
Gastrointestinal disorder subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Throat irritation subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Investigations Blood pressure decreased subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 6		
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 2		
Body temperature increased subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
C-reactive protein increased subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		
Weight increased subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 3		
Injury, poisoning and procedural complications			

Arteriovenous fistula site complication				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Fall				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	2			
Head injury				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Muscle strain				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Post procedural haematoma				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Post procedural haemorrhage				
subjects affected / exposed	2 / 61 (3.28%)			
occurrences (all)	2			
Procedural hypertension				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	6			
Shunt blood flow excessive				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Shunt stenosis				
subjects affected / exposed	2 / 61 (3.28%)			
occurrences (all)	2			
Skin abrasion				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Venous injury				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences (all)	1			
Wound secretion				

subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Hypotonia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Phantom pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
Gastritis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	2		
Gastritis erosive			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Large intestine polyp			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	8 / 61 (13.11%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Skin ulcer			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Pathological fracture			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Soft tissue mass			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	3		
Diabetic gangrene			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Infected skin ulcer			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Injection site abscess			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Postoperative wound infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Pulpitis dental			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Renal cyst infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		

Hyperkalaemia			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Malnutrition			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2013	Modifications to inclusion criteria
20 June 2014	Extension of the clinical phase until Dec 26, 2014
09 October 2014	Extension of the clinical phase until April 30, 2015

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported