Clinical trial results:
A Multicenter Single-arm Extension Study to Describe the Long-term Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis

Summary

EudraCT number	2013-004136-30
Trial protocol	SE IT BE AT ES PT LT PL CZ DK LV DE GR HU NL
Global end of trial date	26 June 2017

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	20130213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02102204
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	26 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to characterize the long-term safety and tolerability of etelcalcetide in the treatment of secondary hyperparathyroidism in subjects with chronic kidney disease (CKD) receiving hemodialysis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), and country-specific regulations/guidelines.
The study protocol and all amendments, the proposed informed consent form, other written subject information, and any proposed advertising materials were reviewed by the applicable independent ethics committee (IEC) or institutional review board (IRB) at each study center. The applicable IEC/IRB provided written approval, and a copy of the approval was received by Amgen before recruitment of subjects into the study and shipment of etelcalcetide.
Before a subject's participation in the clinical study, the investigator at each study center obtained written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any protocol-specific screening procedures or etelcalcetide was administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 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	Australia: 11
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 33
Country: Number of subjects enrolled	Czech Republic: 34
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hungary: 71
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	New Zealand: 4

Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Portugal: 29
Country: Number of subjects enrolled	Russian Federation: 117
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	United States: 326
Worldwide total number of subjects	902
EEA total number of subjects	386

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)	589
From 65 to 84 years	294
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 229 study centers in Europe, Australia, New Zealand, and North America.

Pre-assignment

Screening details:

A total of 902 participants were enrolled in Study 20130213: 215 and 200 participants from the cinacalcet and etelcalcetide groups of the double-blind parent Study 20120360 (2013-000192-33), respectively, and 487 participants from the open-label parent Studies 20120231 (2012-002808-41) and 20120334 (NCT01576146).

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	Etelcalcetide

Arm description:

Participants received etelcalcetide three times a week (TIW) by bolus injection at the end of hemodialysis. The minimum etelcalcetide dose in this study was 2.5 mg and the maximum dose was 15 mg. Etelcalcetide dose was titrated to maintain parathyroid hormone levels within 2x to 9x the upper limit of normal based on the reference range of the assay used at the individual study center.

Arm type	Experimental
Investigational medicinal product name	Etelcalcetide
Investigational medicinal product code	AMG 416
Other name	KAI-4169 Parsabiv
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Etelcalcetide was administered TIW by bolus injection into the venous line of the dialysis circuit at the end of hemodialysis.

Number of subjects in period 1	Etelcalcetide
Started	902
Received Etelcalcetide	884
Completed	603
Not completed	299
Consent withdrawn by subject	137
Death	92
Lost to follow-up	65
Sponsor decision	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Participants were enrolled to receive etelcalcetide three times a week (TIW) by bolus injection at the end of hemodialysis. The minimum etelcalcetide dose in this study was 2.5 mg and the maximum dose was 15 mg. Etelcalcetide dose was titrated to maintain parathyroid hormone levels within 2x to 9x the upper limit of normal based on the reference range of the assay used at the individual study center.

Reporting group values	Overall Study	Total	
Number of subjects	902	902	
Age Categorical Units: Subjects			
Adults (18-64 years)	589	589	
From 65-84 years	294	294	
85 years and over	19	19	
Age Continuous Units: years			
arithmetic mean	57.8		
standard deviation	± 14.3	-	
Gender Categorical Units: Subjects			
Female	365	365	
Male	537	537	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	16	16	
Black (or African American)	195	195	
Native Hawaiian or Other Pacific Islander	9	9	
White	670	670	
Other	11	11	
Ethnicity Units: Subjects			
Hispanic/Latino	79	79	
Not Hispanic/Latino	823	823	
Baseline Parathyroid Hormone Level			
Data are reported for 871 participants with available data.			
Units: pg/mL			
arithmetic mean	522.1		
standard deviation	± 563.9	-	

End points

End points reporting groups

Reporting group title	Etelcalcetide

Reporting group description:

Participants received etelcalcetide three times a week (TIW) by bolus injection at the end of hemodialysis. The minimum etelcalcetide dose in this study was 2.5 mg and the maximum dose was 15 mg. Etelcalcetide dose was titrated to maintain parathyroid hormone levels within 2x to 9x the upper limit of normal based on the reference range of the assay used at the individual study center.

Primary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events[1]

End point description:

A serious adverse event is an AE that met at least 1 of the following criteria:
• fatal
• life threatening
• required in-patient hospitalization or prolongation of existing hospitalization
• resulted in persistent or significant disability/incapacity
• congenital anomaly/birth defect
• other medically important serious event.

The relationship of each AE to study treatment was assessed by the investigator.
The following AE grading scale was used:
Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Moderate: Mild to moderate limitation in activity-some assistance may be needed; no or minimal medical intervention/therapy required
Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible
Life-threatening: Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization probable.

End point type	Primary

End point timeframe:

From the date of first dose of etelcalcetide (in the current study) and up to 30 days after the last dose as of the final analysis data cut-off date of 26 June 2017; median duration of treatment was 563 days.

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 study was descriptive; no formal hypothesis was tested.

End point values	Etelcalcetide			
Subject group type	Reporting group			
Number of subjects analysed	884			
Units: participants				
Any adverse event	768			
Serious adverse events	436			
Treatment-related adverse events	288			
Serious treatment-related adverse events	4			
AEs leading to discontinuation of etelcalcetide	41			
Fatal adverse events	89			
Mild adverse events	122			
Moderate adverse events	219			
Severe adverse events	325			
Life-threatening adverse events	102			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Parathyroid Hormone Levels Between Two to Nine-times the Upper Limit of Normal

End point title	Percentage of Participants With Parathyroid Hormone Levels Between Two to Nine-times the Upper Limit of Normal

End point description:

The percentage of participants who maintained plasma parathyroid hormone (PTH) levels within the Kidney Disease Improving Global Outcomes (KDIGO) recommended range of not less than 2x the upper limit of normal (ULN) and not greater than 9x the ULN at months 6, 12, and 18, with the ULN based on the reference range of the assay used at the individual clinical site.

End point type	Secondary

End point timeframe:

Months 6, 12, and 18

End point values	Etelcalcetide			
Subject group type	Reporting group			
Number of subjects analysed	884[2]			
Units: percentage of participants				
number (confidence interval 95%)				
Month 6 (N = 770)	67.0 (63.6 to 70.3)			
Month 12 (N = 679)	73.2 (69.7 to 76.5)			
Month 18 (N = 540)	71.9 (67.9 to 75.6)			

Notes:

[2] - Participants who received at least 1 dose of etelcalcetide with available data at each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum Phosphorus ≤ the ULN

End point title	Percentage of Participants With Serum Phosphorus ≤ the ULN

End point description:

Percentage of participants with serum phosphorus less than or equal to the upper limit of normal for the assay used.

End point type	Secondary

End point timeframe:

Months 6, 12, and 18

End point values	Etelcalcetide			
Subject group type	Reporting group			
Number of subjects analysed	884			
Units: percentage of participants				
number (confidence interval 95%)				
Month 6 (N = 774)	39.4 (35.9 to 43.0)			
Month 12 (N = 625)	40.0 (36.1 to 44.0)			
Month 18 (N = 478)	36.8 (32.5 to 41.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum Corrected Calcium < 7.5 mg/dL

End point title	Percentage of Participants With Serum Corrected Calcium < 7.5 mg/dL

End point description:

The percentage of participants with serum corrected calcium (cCa) reported for cumulative time intervals from day 1 through months 6, 12, and 18, using the participant's lowest recorded corrected calcium value during the time interval.

If serum albumin was less than 4.0 g/dL, serum calcium was corrected according to the following formula:

cCa (mg/dL) = total calcium (mg/dL) + (4 – albumin [g/dL])*0.8. If serum albumin was > 4.0 g/dL no correction was made.

End point type	Secondary

End point timeframe:

From day 1 to months 6, 12, and 18

End point values	Etelcalcetide			
Subject group type	Reporting group			
Number of subjects analysed	871[3]			
Units: percentage of participants				
number (confidence interval 95%)				
Day 1 to Month 6	9.5 (7.7 to 11.7)			
Day 1 to Month 12	14.1 (11.9 to 16.6)			
Day 1 to Month 18	16.3 (13.9 to 18.9)			

Notes:

[3] - Participants who received at least 1 dose of etelcalcetide with available day 1 data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline Grade 0 or 1 to Postbaseline Grade 3 or 4 for Laboratory Parameters

End point title	Number of Participants With Shifts From Baseline Grade 0 or 1 to Postbaseline Grade 3 or 4 for Laboratory Parameters

End point description:

The Common Terminology Criteria for Adverse Events (CTCAE) grades for laboratory parameter values were defined based on the upper/lower limit of normal from the local laboratories contracted by the study centers

End point type	Secondary

End point timeframe:

Baseline to end of treatment; median duration of treatment was 563 days.

End point values	Etelcalcetide			
Subject group type	Reporting group			
Number of subjects analysed	884[4]			
Units: participants				
Increased Alanine Aminotransferase Grade 1 to 3	1			
Increased Alkaline Phosphatase Grade 1 to 3	2			
Increased Aspartate Aminotransferase Grade 1 to 3	1			
Decreased Corrected Calcium Grade 1 to 3	18			
Decreased Corrected Calcium Grade 1 to 4	2			
Decreased ionized Calcium Grade 1 to 3	1			
Decreased ionized Calcium Grade 1 to 4	2			
Decreased Phosphorous Grade 1 to 3	1			

Notes:

[4] - Participants who received at least 1 dose of etelcalcetide

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Positive Binding Anti-Etelcalcetide Antibodies

End point title	Number of Participants Who Developed Positive Binding Anti-Etelcalcetide Antibodies

End point description:

The number of participants who were binding antibody positive post-baseline with a negative or no result at baseline (where baseline for participants previously treated with etelcalcetide is Day 1 of the first study in which they were exposed to etelcalcetide and for participants previously treated with cinacalcet is the ending time point for study 20120360).

End point type	Secondary

End point timeframe:

Baseline and every 6 months (up to 24 months)

End point values	Etelcalcetide			
Subject group type	Reporting group			
Number of subjects analysed	808[5]			
Units: participants	111			

Notes:

[5] - Participants who received at least 1 dose of etelcalcetide and a post-baseline antibody result

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of etelcalcetide (in the current study) and up to 30 days after the last dose as of the final analysis data cut-off date of 26 June 2017; median duration of treatment was 563 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Etelcalcetide

Reporting group description:

Participants received etelcalcetide three times a week (TIW) by bolus injection at the end of hemodialysis. The minimum etelcalcetide dose in this study was 2.5 mg and the maximum dose was 15 mg. Etelcalcetide dose was titrated to maintain parathyroid hormone levels within 2x to 9x the upper limit of normal based on the reference range of the assay used at the individual study center.

Serious adverse events	Etelcalcetide		
Total subjects affected by serious adverse events			
subjects affected / exposed	436 / 884 (49.32%)		
number of deaths (all causes)	89		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of bladder			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bladder papilloma				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carcinoid tumour of the small bowel				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial adenocarcinoma				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				

subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic dissection			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Aortic stenosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arterial occlusive disease			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Axillary vein thrombosis			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Exsanguination				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extremity necrosis				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	9 / 884 (1.02%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	6 / 884 (0.68%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Hypertensive emergency				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				

subjects affected / exposed	8 / 884 (0.90%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Iliac artery occlusion				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant hypertension				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral artery aneurysm				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery occlusion				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery stenosis				

subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery thrombosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	7 / 884 (0.79%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Steal syndrome			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Superior vena cava stenosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular calcification				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular compression				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous occlusion				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Chest pain				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 4			
Drowning				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Hyperpyrexia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Ischaemic ulcer				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-cardiac chest pain				
subjects affected / exposed	11 / 884 (1.24%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	11 / 884 (1.24%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 4			
Systemic inflammatory response syndrome				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Chronic allograft nephropathy				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transplant rejection				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Benign prostatic hyperplasia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Postmenopausal haemorrhage				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Priapism				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Uterine polyp				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Choking				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cystic lung disease				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dependence on respirator				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	12 / 884 (1.36%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			

Epistaxis			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydrothorax			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	6 / 884 (0.68%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Orthopnoea			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			

subjects affected / exposed	12 / 884 (1.36%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Depression				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Depression suicidal				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Insomnia				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	8 / 884 (0.90%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device dislocation				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device failure				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device malfunction				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device occlusion				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stent malfunction				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis in device				

subjects affected / exposed	6 / 884 (0.68%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood potassium decreased			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paracentesis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral pulse decreased			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula aneurysm			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula occlusion			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Arteriovenous fistula site complication			
subjects affected / exposed	11 / 884 (1.24%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula thrombosis			
subjects affected / exposed	24 / 884 (2.71%)		
occurrences causally related to treatment / all	0 / 27		
deaths causally related to treatment / all	0 / 1		
Arteriovenous graft site haemorrhage			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous graft thrombosis			
subjects affected / exposed	9 / 884 (1.02%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Craniocerebral injury			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	7 / 884 (0.79%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Joint dislocation			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Patella fracture				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Post-traumatic pain				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural hypertension				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural hypotension				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Procedural intestinal perforation				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shunt aneurysm				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shunt occlusion				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Shunt stenosis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Subdural haematoma				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheostomy malfunction				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular access complication				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Vascular access malfunction				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular graft complication				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular graft occlusion				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular injury				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular pseudoaneurysm ruptured				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound dehiscence				

subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic arteriovenous malformation			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Porencephaly			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	13 / 884 (1.47%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 3		
Angina pectoris			
subjects affected / exposed	8 / 884 (0.90%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Aortic valve incompetence			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic valve stenosis			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	15 / 884 (1.70%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 1		
Atrial flutter			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	20 / 884 (2.26%)		
occurrences causally related to treatment / all	0 / 21		
deaths causally related to treatment / all	0 / 15		
Cardiac failure			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	8 / 884 (0.90%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Cardiac valve disease				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 3			
Cardiogenic shock				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cardiomyopathy				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 3			
Myocardial ischaemia				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Pericardial effusion				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pericarditis uraemic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus node dysfunction				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				

subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain injury			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Brain stem stroke			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery occlusion			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Carpal tunnel syndrome			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			

subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Cerebral infarction				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 2			
Diabetic neuropathy				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dysaesthesia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				

subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Facial paresis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersomnia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypoxic-ischaemic encephalopathy				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metabolic encephalopathy				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuritis cranial				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Normal pressure hydrocephalus				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Quadriplegia				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	13 / 884 (1.47%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Transient global amnesia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uraemic neuropathy				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	19 / 884 (2.15%)			
occurrences causally related to treatment / all	0 / 26			
deaths causally related to treatment / all	0 / 1			
Coagulopathy				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic anaemia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrogenic anaemia				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cataract				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Optic ischaemic neuropathy				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vision blurred				

subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	7 / 884 (0.79%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic gastritis			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Constipation			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epigastric discomfort				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis haemorrhagic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroduodenitis				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic erosive gastritis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hernial eventration				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Inguinal hernia				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Intestinal obstruction				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Large intestinal obstruction				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic disorder				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pancreatitis chronic				

subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haemorrhage				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestine polyp				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	6 / 884 (0.68%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	5 / 884 (0.57%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Acute hepatic failure				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct stone				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Biliary colic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Cholecystitis chronic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gallbladder disorder				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cyst				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cyst ruptured				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver injury				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sphincter of Oddi dysfunction				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Diabetic foot				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Skin discolouration				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

End stage renal disease				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haematuria				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cyst				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Renal cyst haemorrhage				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal vein thrombosis				

subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urethral stenosis			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Goitre			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperparathyroidism tertiary			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 884 (0.68%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Arthritis reactive			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Back pain			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cervical spinal stenosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chondrocalcinosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture nonunion			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscle spasms			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscle swelling			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			

subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathic arthropathy			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	6 / 884 (0.68%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Pseudarthrosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SLE arthritis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon calcification				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall abscess				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site infection				

subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Arteriovenous graft site abscess				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriovenous graft site infection				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Bacteraemia				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	10 / 884 (1.13%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 1			
Bronchitis bacterial				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	9 / 884 (1.02%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Cellulitis gangrenous				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis orbital				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Citrobacter sepsis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				

subjects affected / exposed	4 / 884 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetic foot infection				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetic gangrene				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 2			
Epiglottitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				

subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	9 / 884 (1.02%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Helicobacter gastritis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis A				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Intestinal tuberculosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver abscess			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mediastinitis			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle abscess				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orchitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	11 / 884 (1.24%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 1			
Osteomyelitis chronic				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perineal abscess				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	40 / 884 (4.52%)			
occurrences causally related to treatment / all	0 / 48			
deaths causally related to treatment / all	0 / 6			
Post procedural infection				

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomembranous colitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	7 / 884 (0.79%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	27 / 884 (3.05%)			
occurrences causally related to treatment / all	0 / 29			
deaths causally related to treatment / all	0 / 8			
Septic shock				

subjects affected / exposed	14 / 884 (1.58%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 5		
Serratia bacteraemia			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Staphylococcal sepsis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stoma site infection			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Systemic infection			

subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheobronchitis				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	6 / 884 (0.68%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	3 / 884 (0.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Vascular access site infection				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	2 / 884 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vulval abscess				
subjects affected / exposed	1 / 884 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				

subjects affected / exposed	3 / 884 (0.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Calciphylaxis			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Electrolyte imbalance			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	16 / 884 (1.81%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 0		
Fluid retention			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperinsulinaemic hypoglycaemia			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			

subjects affected / exposed	16 / 884 (1.81%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 0		
Hypervolaemia			
subjects affected / exposed	2 / 884 (0.23%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	4 / 884 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 884 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Etelcalcetide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	537 / 884 (60.75%)		
Investigations			
Blood calcium decreased			
subjects affected / exposed	253 / 884 (28.62%)		
occurrences (all)	408		
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	45 / 884 (5.09%)		
occurrences (all)	71		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	62 / 884 (7.01%) 88 60 / 884 (6.79%) 108		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 84 / 884 (9.50%) 112 58 / 884 (6.56%) 70 56 / 884 (6.33%) 71		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 51 / 884 (5.77%) 63 50 / 884 (5.66%) 63		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 52 / 884 (5.88%) 58 73 / 884 (8.26%) 122 59 / 884 (6.67%) 85		
Infections and infestations Upper respiratory tract infection			

subjects affected / exposed	58 / 884 (6.56%)		
occurrences (all)	73		
Viral upper respiratory tract infection			
subjects affected / exposed	45 / 884 (5.09%)		
occurrences (all)	74		
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	82 / 884 (9.28%)		
occurrences (all)	99		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2014	The primary reason for the protocol amendment was both to create greater flexibility in dose titration in a real-world setting while recognizing differences in practice patterns across centers and regions and to standardize certain measurements. Changes to the protocol included: • A minimum monthly calcium and albumin was mandated because there are slight differences in standards of care globally for frequency of selected laboratory assays. These values allowed for a consistent calcium value to use in analyses. • Flexibility was allowed in the type of calcium measurement allowed (ie, corrected calcium or total calcium or ionized calcium equivalent) to inform dose titration. • The titration algorithm was modified to allow for increased flexibility for dose reductions in increments of 2.5 mg at the discretion of the investigator, based on corrected calcium values and not just parathyroid hormone values. • The titration algorithm was modified to allow for increased flexibility in the use of oral calcium supplements and the dialysate calcium bath. • The starting dose was modified only for subjects entering from Study 20120360 to 2.5 mg instead of 5 mg (all other subjects entered without a treatment gap from an open-label study, continuing on the same dose). • "Velcalcetide" was replaced with AMG 416.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported