Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis

Summary

EudraCT number	2012-002805-23
Trial protocol	HU BE CZ GB IT DE ES AT
Global end of trial date	12 June 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	20120229 (KAI-4169-006)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01785849
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	12 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of AMG 416 in the treatment of secondary hyperparathyroidism (SHPT) in subjects with chronic kidney disease (CKD) on hemodialysis. Primary: To evaluate the efficacy of AMG 416 compared with placebo for reducing the serum intact parathyroid hormone level (iPTH) by > 30%.

Protection of trial subjects:

This study was conducted in accordance with applicable country regulations and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy:

All subjects, regardless of treatment assignment, received standard of care which could have included calcium supplements, vitamin D sterols, nutritional vitamin D, and phosphate binders, as prescribed by the individual investigator.

Evidence for comparator: -

Actual start date of recruitment	12 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 250
Country: Number of subjects enrolled	Australia: 15

Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Russian Federation: 38
Worldwide total number of subjects	508
EEA total number of subjects	188

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)	332
From 65 to 84 years	166
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 111 centers in the US, Canada, Europe, Israel, Russian Federation, and Australia. The first subject was enrolled on 12 March 2013 and the last subject enrolled on 08 November 2013.

Pre-assignment

Screening details:

Before randomization, subjects entered a screening period of up to 8 weeks to determine eligibility. Eligible subjects were randomized in a ratio of 1:1 to AMG 416 or placebo. Randomization was stratified by mean screening PTH (< 600 pg/mL, 600 to ≤ 1000 pg/mL, and > 1000 pg/mL), prior cinacalcet use and region (North America or non-North America).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo administered by intravenous bolus injection at the end of each hemodialysis session, three times per week (TIW) for 26 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously (IV) three times per week.

Arm title	AMG 416

Arm description:

Subjects received AMG 416 administered by intravenous bolus injection at the end of each hemodialysis session, TIW, for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	AMG 416
Investigational medicinal product code	AMG 416
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously three times per week. The starting dose of AMG 416 was 5 mg. The dose may have been increased at 4-week intervals by 2.5 mg or 5 mg on the basis of the predialysis PTH and corrected calcium concentrations obtained in the prior week. The minimum dose was 2.5 mg and the maximum dose was 15 mg.

Number of subjects in period 1	Placebo	AMG 416
Started	254	254
Received Treatment	254	251
Completed	193	220
Not completed	61	34
Consent withdrawn by subject	15	12
Protocol specified criteria	29	1
Death	7	9
Lost to follow-up	10	11
Sponsor decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo administered by intravenous bolus injection at the end of each hemodialysis session, three times per week (TIW) for 26 weeks.	
Reporting group title	AMG 416
Reporting group description:	
Subjects received AMG 416 administered by intravenous bolus injection at the end of each hemodialysis session, TIW, for 26 weeks.	

Reporting group values	Placebo	AMG 416	Total
Number of subjects	254	254	508
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.1	58.4	
standard deviation	± 14.5	± 14.6	-
Gender categorical Units: Subjects			
Female	114	103	217
Male	140	151	291
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	5	8
Black (or African American)	69	72	141
Native Hawaiian or Other Pacific Islander	2	0	2
White	175	173	348
Other	4	4	8
Missing	1	0	1
Mean screening serum intact parathyroid hormone (iPTH) Units: Subjects			
< 600 pg/mL	84	87	171
>= 600 to <= 1000 pg/mL	114	115	229
> 1000 pg/mL	56	52	108
Recent cinacalcet use within 8 weeks prior to randomization Units: Subjects			
Yes	34	33	67
No	220	221	441
Region Units: Subjects			
North America	129	132	261
Non-North America	125	122	247

Parathyroid Hormone (PTH) Units: pg/mL arithmetic mean standard deviation	 819.7 ± 386	 848.7 ± 520.4	 -
Corrected Calcium Units: mg/dL arithmetic mean standard deviation	 9.61 ± 0.6	 9.65 ± 0.66	 -
Phosphorus			
Data available for 250 subjects in each treatment group.			
Units: mg/dL arithmetic mean standard deviation	 5.78 ± 1.6	 5.95 ± 1.59	 -
corrected calcium phosphorus product (cCa x P)			
Data available for 249 and 250 subjects in each treatment group respectively.			
Units: mg^2/dL^2 arithmetic mean standard deviation	 55.54 ± 15.81	 57.37 ± 15.51	 -

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo administered by intravenous bolus injection at the end of each hemodialysis session, three times per week (TIW) for 26 weeks.	
Reporting group title	AMG 416
Reporting group description:	
Subjects received AMG 416 administered by intravenous bolus injection at the end of each hemodialysis session, TIW, for 26 weeks.	

Primary: Percentage of Subjects With > 30% Decrease From Baseline in Mean PTH During the Efficacy Assessment Phase

End point title	Percentage of Subjects With > 30% Decrease From Baseline in Mean PTH During the Efficacy Assessment Phase
End point description:	
Subjects who did not have any scheduled assessments during the EAP were considered as nonresponders.	
End point type	Primary
End point timeframe:	
Baseline and the efficacy assessment phase (EAP; defined as Weeks 20 to 27, inclusive).	

End point values	Placebo	AMG 416		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254[1]	254[2]		
Units: percentage of subjects				
number (not applicable)	8.3	74		

Notes:

[1] - Full analysis set

[2] - Full analysis set

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
A Cochran-Mantel-Haenszel test stratified by screening PTH category (< 600, ≥ 600 to ≤ 1000, and > 1000 pg/mL), recent cinacalcet use within 8 weeks before randomization (yes and no), and region (North America and non-North America) was used to compare the primary endpoint of proportion of subjects with > 30% reduction from baseline in PTH during the EAP between AMG 416 and placebo.	
Comparison groups	AMG 416 v Placebo
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	32.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	18.71
upper limit	56.31

Secondary: Percentage of Subjects With Predialysis Parathyroid Hormone ≤ 300 pg/mL During the Efficacy Assessment Phase

End point title	Percentage of Subjects With Predialysis Parathyroid Hormone ≤ 300 pg/mL During the Efficacy Assessment Phase

End point description:

Subjects who had no scheduled assessments during the EAP were considered to be non-responders.

End point type	Secondary

End point timeframe:

Baseline and the efficacy assessment phase (Week 20 to Week 27)

End point values	Placebo	AMG 416		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	254		
Units: percentage of subjects				
number (not applicable)	5.1	49.6		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Stratification factors based on screening PTH level, prior cinacalcet use within 8 weeks prior to randomization, and region.

Comparison groups	Placebo v AMG 416
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	22.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.47
upper limit	42.48

Secondary: Percent Change From Baseline in Predialysis PTH During the Efficacy Assessment Phase

End point title	Percent Change From Baseline in Predialysis PTH During the Efficacy Assessment Phase

End point description:

End point type	Secondary

End point timeframe:

Baseline and the Efficacy Assessment Phase (Week 20 to Week 27)

End point values	Placebo	AMG 416		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219[3]	229[4]		
Units: percent change				
arithmetic mean (standard error)	13 (± 2.81)	-55.11 (± 1.94)		

Notes:

[3] - Full analysis set subjects with observed data

[4] - Full analysis set subjects with observed data

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Mixed-effects model includes treatment, stratification factors, visit, and treatment by visit interaction as covariates.

Comparison groups	AMG 416 v Placebo
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-71.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.77
upper limit	-64.46
Variability estimate	Standard error of the mean
Dispersion value	3.39

Secondary: Percent Change From Baseline in Predialysis Corrected Calcium During the Efficacy Assessment Phase

End point title	Percent Change From Baseline in Predialysis Corrected Calcium During the Efficacy Assessment Phase

End point description:

End point type	Secondary

End point timeframe:

Baseline and the efficacy assessment phase (Week 20 to Week 27)

End point values	Placebo	AMG 416		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219[5]	229[6]		
Units: percent change				
arithmetic mean (standard error)	1.18 (± 0.29)	-7.29 (± 0.53)		

Notes:

[5] - Full analysis set subjects with observed data

[6] - Full analysis set subjects with observed data

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Mixed-effects model includes treatment, stratification factors, visit, and treatment by visit interaction as covariates.

Comparison groups	Placebo v AMG 416
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-8.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.52
upper limit	-7.23
Variability estimate	Standard error of the mean
Dispersion value	0.58

Secondary: Percent Change From Baseline in Predialysis Corrected Calcium Phosphorus Product During the Efficacy Assessment Phase

End point title	Percent Change From Baseline in Predialysis Corrected Calcium Phosphorus Product During the Efficacy Assessment Phase

End point description:

End point type	Secondary

End point timeframe:

Baseline and the efficacy assessment phase (Week 20 to Week 27)

End point values	Placebo	AMG 416		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213[7]	227[8]		
Units: percent change				
arithmetic mean (standard error)	-0.19 (± 1.44)	-14.34 (± 2.06)		

Notes:

[7] - Full analysis set subjects with observed data

[8] - Full analysis set subjects with observed data

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
Mixed-effects model included treatment, stratification factors, visit, and treatment by visit interaction as covariates.	
Comparison groups	Placebo v AMG 416
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-14.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.73
upper limit	-10.25
Variability estimate	Standard error of the mean
Dispersion value	2.41

Secondary: Percent Change From Baseline in Predialysis Phosphorus During the Efficacy Assessment Phase

End point title	Percent Change From Baseline in Predialysis Phosphorus During the Efficacy Assessment Phase
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and the efficacy assessment phase (Week 20 to Week 27)	

End point values	Placebo	AMG 416		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214[9]	227[10]		
Units: percent change				
arithmetic mean (standard error)	-1.31 (± 1.42)	-7.71 (± 2.16)		

Notes:

[9] - Full analysis set subjects with observed data

[10] - Full analysis set subjects with observed data

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Mixed-effects model included treatment, stratification factors, visit, and treatment by visit interaction as covariates.

Comparison groups	Placebo v AMG 416
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-7.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.31
upper limit	-2.59
Variability estimate	Standard error of the mean
Dispersion value	2.47

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 until 30 days after the last dose; the treatment period was 26 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo administered by intravenous bolus injection at the end of each hemodialysis session, three times per week (TIW) for 26 weeks.	
Reporting group title	AMG 416
Reporting group description:	
Subjects received AMG 416 administered by intravenous bolus injection at the end of each hemodialysis session, TIW, for 26 weeks.	

Serious adverse events	Placebo	AMG 416	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 254 (30.71%)	68 / 251 (27.09%)	
number of deaths (all causes)	7	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Biliary cancer metastatic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bone giant cell tumour benign			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure fluctuation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatosis with polyangiitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 254 (0.79%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular rupture			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stenosis			

subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous stenosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chills			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Device issue			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			

subjects affected / exposed	0 / 254 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 254 (0.79%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 254 (1.18%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 254 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			

subjects affected / exposed	3 / 254 (1.18%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 254 (0.79%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			

subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery restenosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirenal haematoma			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Scapula fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 254 (0.39%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aortic valve stenosis			
subjects affected / exposed	0 / 254 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 254 (1.57%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 254 (0.39%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 254 (0.79%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 254 (0.79%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic cerebral infarction			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 254 (1.57%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal telangiectasia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth impacted			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abscess limb			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			

subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gangrene			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 254 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	4 / 254 (1.57%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	3 / 254 (1.18%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic embolus			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 254 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subacute endocarditis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 254 (0.79%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	5 / 254 (1.97%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 254 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 254 (0.39%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	2 / 254 (0.79%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	AMG 416	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 254 (43.31%)	194 / 251 (77.29%)	
Investigations			
Blood calcium decreased			
subjects affected / exposed	21 / 254 (8.27%)	153 / 251 (60.96%)	
occurrences (all)	26	240	
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	14 / 254 (5.51%)	11 / 251 (4.38%)	
occurrences (all)	18	17	
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 254 (6.30%)	12 / 251 (4.78%)	
occurrences (all)	19	21	
Hypotension			
subjects affected / exposed	10 / 254 (3.94%)	14 / 251 (5.58%)	
occurrences (all)	11	14	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 254 (7.87%)	18 / 251 (7.17%)	
occurrences (all)	26	22	
Paraesthesia			
subjects affected / exposed	3 / 254 (1.18%)	13 / 251 (5.18%)	
occurrences (all)	5	24	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 254 (6.69%)	18 / 251 (7.17%)	
occurrences (all)	19	18	
Nausea			
subjects affected / exposed	13 / 254 (5.12%)	31 / 251 (12.35%)	
occurrences (all)	20	38	
Vomiting			
subjects affected / exposed	18 / 254 (7.09%)	25 / 251 (9.96%)	
occurrences (all)	23	29	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	18 / 254 (7.09%)	30 / 251 (11.95%)	
occurrences (all)	20	36	
Pain in extremity			
subjects affected / exposed	11 / 254 (4.33%)	17 / 251 (6.77%)	
occurrences (all)	11	21	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 254 (5.12%)	11 / 251 (4.38%)	
occurrences (all)	15	11	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 254 (0.39%)	18 / 251 (7.17%)	
occurrences (all)	1	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2013	- Allowed initiation of AMG 416 administration Monday-Friday, instead of the previous restriction of Wednesday or Thursday only. - Clarified that AMG 416 should not be administered subcutaneously or via any other route other than IV, and that it should not be administered concurrently with other IV medications. - Clarified that if suspended for symptomatic hypocalcemia, dosing should only resume after checking cCa concentrations, in addition to the currently stated resolution of symptomatic hypocalcemia. - Allowed adjustment of vitamin D for hypocalcemia during the study. - Provided a recommended sequence of interventions for treating hypocalcemia with reference to modification of oral calcium supplements, dialysate calcium concentration, and then vitamin D. - Change specification that postdialysis blood samples must be collected after the postdialysis ECG, to now be collected before the ECG sequence. - Expand the postdialysis ECG and blood sample collection window from the previous 15 to 30 minutes postdose, to now be 10 to 60 minutes postdose. - Provided a sample "Serious Adverse Event Form" as Appendix D - Pregnancy testing for women of childbearing potential was increased from the previous 2 times in total (before study start and at end of study), to be 4 times in total (every 12 weeks).
03 September 2013	- Removed requirement for male contraception in the entry criteria to reflect updated core risks and discomforts safety language - Included updated standard safety language on instructions for reporting serious adverse events after the 30-day follow-up visit - Included updated standard safety language on the shortened notification period for pregnancy and lactation reporting from the original 7 days to now be within 24 hours - Removed blinding of postdialysis ECG results

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported