



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	2012-002806-31
Trial protocol	BE CZ IT ES SE HU PL NL DE
Global end of trial date	12 May 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	20120230 (KAI-4169-007)
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01788046
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 May 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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	Netherlands: 12
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 283
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Israel: 9

Country: Number of subjects enrolled	Russian Federation: 20
Worldwide total number of subjects	515
EEA total number of subjects	173

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)	334
From 65 to 84 years	171
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 97 centers in the US, Canada, Europe, Israel, the Russian Federation, and Australia. The first subject was enrolled on 12 March 2013, and the last subject 07 October 2013.

Pre-assignment

Screening details:

Prior to randomization, subjects entered a screening period of up to 8 weeks to determine eligibility. Eligible subjects were randomized 1:1 to receive AMG 416 or placebo. Randomization was stratified by 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/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Administered intravenously (IV) three times per week.

Arm title	AMG 416
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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/infusion
Routes of administration	Intravenous bolus 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 maximum dose was 15 mg.

Number of subjects in period 1	Placebo	AMG 416
Started	260	255
Received Treatment	259	252
Completed	204	218
Not completed	56	37
Consent withdrawn by subject	12	12
Protocol specified criteria	25	1
Death	7	5
Lost to follow-up	12	19

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	260	255	515
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59	58.4	
standard deviation	± 13.9	± 14.6	-
Gender categorical Units: Subjects			
Female	95	93	188
Male	165	162	327
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	13	19
Black (or African American)	80	64	144
Native Hawaiian or Other Pacific Islander	3	7	10
White	169	163	332
Other	2	6	8
Missing	0	2	2
Mean screening serum intact parathroid hormone (iPTH) Units: Subjects			
< 600 pg/mL	84	84	168
>= 600 to <= 1000 pg/mL	121	118	239
> 1000 pg/mL	55	53	108
Recent cinacalcet use within 8 weeks prior to randomization Units: Subjects			
Yes	33	29	62
No	227	226	453
Region Units: Subjects			
North America	150	146	296
Non-North America	110	109	219

Parathyroid hormone Units: pg/mL arithmetic mean standard deviation	851.7 ± 552	845 ± 464.3	-
Corrected calcium (cCa) Units: mg/dL arithmetic mean standard deviation	9.7 ± 0.69	9.63 ± 0.65	-
Phosphorus			
Data available for 257 and 251 subjects in each treatment group respectively			
Units: mg/dL arithmetic mean standard deviation	5.83 ± 1.45	5.76 ± 1.6	-
Corrected calcium phosphorus product (cCa x P)			
Data available for 257 and 251 subjects in each treatment group respectively			
Units: mg ² /dL ² arithmetic mean standard deviation	56.37 ± 14.5	55.3 ± 15.27	-

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	260 ^[1]	255 ^[2]		
Units: percentage of subjects				
number (not applicable)	9.6	75.3		

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	Placebo v AMG 416
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	30.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	18.18
upper limit	52.17

Secondary: Percentage of Subjects Achieving Mean PTH $\leq$ 300 pg/mL During the Efficacy Assessment Phase

End point title	Percentage of Subjects Achieving Mean PTH $\leq$ 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	260	255		
Units: percentage of subjects				
number (not applicable)	4.6	53.3		

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	515
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	33.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.35
upper limit	70.37

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
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End point description:

End point type	Secondary
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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	237 ^[3]	227 ^[4]		
Units: percent change				
arithmetic mean (standard error)	13.72 ($\pm$ 2.5)	-57.39 ($\pm$ 1.91)		

Notes:

[3] - Full analysis set subjects with observed data

[4] - Full analysis set subjects with observed data

Statistical analyses

Statistical analysis title	Primary Analysis
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Statistical analysis description:

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

Comparison groups	Placebo v AMG 416
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Number of subjects included in analysis	464
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.001
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Method	Mixed models analysis
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Parameter estimate	Mean difference
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Point estimate	-71.34
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-77.53
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upper limit	-65.14
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Variability estimate	Standard error of the mean
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Dispersion value	3.15
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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
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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	237 ^[5]	227 ^[6]		
Units: percent change				
arithmetic mean (standard error)	0.58 (± 0.29)	-6.69 (± 0.55)		

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 included treatment, stratification factors, visit, and treatment by visit interaction as covariates.	
Comparison groups	Placebo v AMG 416
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.38
upper limit	-6.03
Variability estimate	Standard error of the mean
Dispersion value	0.6

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	234 ^[7]	223 ^[8]		
Units: percent change				
arithmetic mean (standard error)	-1.06 (± 1.42)	-15.84 (± 1.57)		

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	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-14.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.65
upper limit	-10.51
Variability estimate	Standard error of the mean
Dispersion value	2.07

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	234 ^[9]	223 ^[10]		
Units: percent change				
arithmetic mean (standard error)	-1.6 (± 1.42)	-9.63 (± 1.61)		

Notes:

[9] - Full analysis set subjects with available data

[10] - Full analysis set subjects with available 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	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference
Point estimate	-8.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.15
upper limit	-3.92
Variability estimate	Standard error of the mean
Dispersion value	2.09

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	AMG 416
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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 title	Placebo
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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.

Serious adverse events	AMG 416	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 252 (24.60%)	71 / 259 (27.41%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor peripheral circulation			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombophlebitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous stenosis			

subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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			
Asthenia			
subjects affected / exposed	0 / 252 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haematoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia obstructive			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 252 (0.40%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 252 (1.19%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Surgical failure			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 252 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 252 (0.79%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 252 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	2 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Electrocardiogram T wave inversion subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula aneurysm subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula occlusion subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haematoma subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis subjects affected / exposed	2 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Burns second degree			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (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	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft complication			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure			

subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural vomiting			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin graft failure			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	2 / 252 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			

subjects affected / exposed	2 / 252 (0.79%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 252 (1.19%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 252 (0.40%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 252 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			

subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 252 (0.79%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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	2 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 252 (0.40%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemic seizure			

subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	0 / 252 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 252 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 252 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 252 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 252 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathic ulcer			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ulcer			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpable purpura			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (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 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			

subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urethral stenosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Primary hyperaldosteronism			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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			
Arthralgia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 252 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle twitching			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			

subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 252 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile sepsis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 252 (0.40%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningoencephalitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 252 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 252 (1.59%)	10 / 259 (3.86%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 252 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis syndrome			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin graft infection			

subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
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 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral myocarditis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	2 / 252 (0.79%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	6 / 252 (2.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypervolaemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	2 / 252 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	1 / 252 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	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	AMG 416	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	200 / 252 (79.37%)	133 / 259 (51.35%)	
Investigations			
Blood calcium decreased			
subjects affected / exposed	168 / 252 (66.67%)	31 / 259 (11.97%)	
occurrences (all)	299	35	
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	16 / 252 (6.35%)	12 / 259 (4.63%)	
occurrences (all)	18	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 252 (7.14%)	12 / 259 (4.63%)	
occurrences (all)	24	17	
Hypotension			

subjects affected / exposed occurrences (all)	14 / 252 (5.56%) 21	15 / 259 (5.79%) 18	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	20 / 252 (7.94%) 21	11 / 259 (4.25%) 16	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 252 (3.17%) 8	13 / 259 (5.02%) 18	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	35 / 252 (13.89%) 40 23 / 252 (9.13%) 28 19 / 252 (7.54%) 19	25 / 259 (9.65%) 42 18 / 259 (6.95%) 21 8 / 259 (3.09%) 8	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	10 / 252 (3.97%) 10	15 / 259 (5.79%) 15	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	11 / 252 (4.37%) 12 14 / 252 (5.56%) 17 28 / 252 (11.11%) 47	15 / 259 (5.79%) 15 9 / 259 (3.47%) 10 16 / 259 (6.18%) 25	
Infections and infestations			

Bronchitis			
subjects affected / exposed	7 / 252 (2.78%)	3 / 259 (1.16%)	
occurrences (all)	9	3	
Upper respiratory tract infection			
subjects affected / exposed	13 / 252 (5.16%)	15 / 259 (5.79%)	
occurrences (all)	13	16	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	17 / 252 (6.75%)	0 / 259 (0.00%)	
occurrences (all)	17	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 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 corrected calcium 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. - 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).
04 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported