



## Clinical trial results:

### Efficacy and tolerability of nicotinamide as add-on therapy compared to placebo in dialysis-dependent patients with hyperphosphatemia

#### Summary

EudraCT number	2013-000488-95
Trial protocol	DE PL AT HU
Global end of trial date	14 March 2017

#### Results information

Result version number	v1 (current)
This version publication date	20 October 2018
First version publication date	20 October 2018

#### Trial information

##### Trial identification

Sponsor protocol code	6520-9961-04
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	MEDICE Arzneimittel Pütter GmbH & Co. KG
Sponsor organisation address	Kuhloweg 37, Iserlohn, Germany, 58638
Public contact	Medizinische Abteilung, MEDICE Arzneimittel Pütter GmbH & Co. KG, +49 2371937523, b.hellmann@medice.de
Scientific contact	Medizinische Abteilung, MEDICE Arzneimittel Pütter GmbH & Co. KG, +49 2371937523, b.hellmann@medice.de

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	09 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2017
Global end of trial reached?	Yes
Global end of trial date	14 March 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

Nicotinamide MR compared to placebo as an add-on therapy to approved individual phosphate binders in the long term reduction of elevated phosphate levels in haemodialysis patients

Protection of trial subjects:

The investigator should have discontinued the study medication for the following reasons:

- Lack of efficacy of the study medication even after rescue therapies
- Occurring of intolerable adverse effects even after dose reduction
- Platelet count less than 75/nl
- Creatine kinase increased  $\geq 5$  times the normal range
- Transaminase (AST, ALT) increased  $\geq 3$  times the normal range
- Use of medications/drugs not prescribed or allowed by the investigator and/or not permitted during the trial

- Onset of pregnancy
- Suspected relevant drug interaction(s)
- Subsequent ascertainment of non-fulfilment of the inclusion criteria or fulfilment of the exclusion criteria

- Continued trial participation unacceptable/unreasonable in the opinion of the investigator

Background therapy:

Unmodified phosphate binding therapy with one or two phosphate binders for at least 1 month prior to screening

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Poland: 133
Country: Number of subjects enrolled	Austria: 83
Country: Number of subjects enrolled	Germany: 507
Worldwide total number of subjects	723
EEA total number of subjects	723

Notes:

<b>Subjects enrolled per age group</b>	
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)	507
From 65 to 84 years	216
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Male and female patients >18 years on stable hemodialysis since at least 6 month were included at the study site

### Pre-assignment

Screening details:

1076 patients were screened in this clinical trial and of these 738 patients were randomised.

### Period 1

Period 1 title	Efficacy and Safety Evaluation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Placebo capsules were identical to verum. Laboratory measurement of serum nicotinamide and its metabolite concentrations were transferred to data management not before unblinding.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nicotinamide

Arm description:

Verum

Arm type	Experimental
Investigational medicinal product name	Nicotinamide MR 250 mg capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage was titrated depending on serum phosphate concentrations between 1 and 6 capsules per day. Once daily intake at bed time or twice daily intake after wakeup and at bedtime.

<b>Arm title</b>	Placebo
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Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage was titrated depending on serum phosphate concentrations between 1 and 6 capsules per day. Once daily intake at bed time or twice daily intake after wakeup and at bedtime.

<b>Number of subjects in period 1</b>	Nicotinamide	Placebo
Started	540	183
Completed	402	144
Not completed	138	39
Adverse event, serious fatal	24	9
Consent withdrawn by subject	34	9
Adverse event, non-fatal	27	3
Renal transplantation	40	16
Lack of compliance	3	2
Lost to follow-up	6	-
Protocol deviation	4	-

## Baseline characteristics

### Reporting groups

Reporting group title	Efficacy and Safety Evaluation
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Reporting group description: -

Reporting group values	Efficacy and Safety Evaluation	Total	
Number of subjects	723	723	
Age categorical			
Units: Subjects			
Adults (18-64 years)	405	405	
From 65-84 years	298	298	
85 years and over	20	20	
Age continuous			
Units: years			
arithmetic mean	61.9		
standard deviation	± 13.92	-	
Gender categorical			
Units: Subjects			
Female	268	268	
Male	455	455	

### Subject analysis sets

Subject analysis set title	Safety Population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety population includes all randomized patients who took the study medication at least once

Subject analysis set title	Intention to Treat Population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Safety population with the exclusion of one legally impaired patient.

Subject analysis set title	Per Protocol Population
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Subject analysis set type	Per protocol
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Subject analysis set description:

Patients of the Intention to treat with one of the following protocol deviations:

- Lack of compliance (less than 75% or more than 125% of the prescribed daily dose either during the whole study or in 2 consecutive study visits [week 0 to week 12 or between week 8 and week 12])
- Study medication was temporarily withdrawn for > 14 days between week 0 and week 8
- Retrospectively identified violation of inclusion/exclusion criteria at screening
- Incorrect study medication dispensed (randomization violated)
- Unblinding
- Confusion/mix up of provided study medication
- Drop-out (study medication withdrawn or entire study stopped) before week 12

Subject analysis set title	Completers population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All patients of the Per protocol population that neither terminated study medication intake permanently nor study participation prematurely (i.e. before week 52) and who had a record for serum phosphate at week 52 irrespective of whether the phosphate value at screening was missing.

Reporting group values	Safety Population	Intention to Treat Population	Per Protocol Population
Number of subjects	723	722	439
Age categorical Units: Subjects			
Adults (18-64 years)	405		
From 65-84 years	298		
85 years and over	20		
Age continuous Units: years			
arithmetic mean	61.9	61.8	61.0
standard deviation	± 13.92	± 13.92	± 13.34
Gender categorical Units: Subjects			
Female	268	267	151
Male	455	455	288

Reporting group values	Completers population		
Number of subjects	358		
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	61.1		
standard deviation	± 13.62		
Gender categorical Units: Subjects			
Female	123		
Male	235		

## End points

### End points reporting groups

Reporting group title	Nicotinamide
Reporting group description:	
Verum	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population includes all randomized patients who took the study medication at least once	
Subject analysis set title	Intention to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Safety population with the exclusion of one legally impaired patient.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients of the Intention to treat with one of the following protocol deviations:	
<ul style="list-style-type: none"><li>• Lack of compliance (less than 75% or more than 125% of the prescribed daily dose either during the whole study or in 2 consecutive study visits [week 0 to week 12 or between week 8 and week 12])</li><li>• Study medication was temporarily withdrawn for &gt; 14 days between week 0 and week 8</li><li>• Retrospectively identified violation of inclusion/exclusion criteria at screening</li><li>• Incorrect study medication dispensed (randomization violated)</li><li>• Unblinding</li><li>• Confusion/mix up of provided study medication</li><li>• Drop-out (study medication withdrawn or entire study stopped) before week 12</li></ul>	
Subject analysis set title	Completers population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients of the Per protocol population that neither terminated study medication intake permanently nor study participation prematurely (i.e. before week 52) and who had a record for serum phosphate at week 52 irrespective of whether the phosphate value at screening was missing.	

### Primary: Serum Phosphate (Intention to Treat Population)

End point title	Serum Phosphate (Intention to Treat Population)
End point description:	
<p>The primary criterion of this study was the serum phosphate concentration in mg/dL at W12 for the ITT population. The analysis was based on a linear mixed model to also address the stratification factors of the randomization. The factors/covariates study medication group, study site, individual additional phosphate binder (phosphate binder containing calcium, lanthanum carbonate and aluminum, and other phosphate binders) and initial value of phosphate (screening) were considered. The study medication group was included as a fixed effect; the study site was modelled as random effect (random intercept). The initial value of phosphate and the individual additional phosphate binder(s) were included as fixed effect covariates. Interactions were not considered in the primary model. The claim of superiority was based on a two-sided p-value related to the Wald-type test statistic for the treatment effect applying a two-sided significance concentration of 2.5%.</p>	
End point type	Primary
End point timeframe:	
12 weeks	



<b>End point values</b>	Nicotinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	499	174		
Units: mg/dL				
arithmetic mean (standard deviation)	5.36 (± 1.382)	5.88 (± 1.319)		

## Statistical analyses

<b>Statistical analysis title</b>	Primary Endpoint Serum Phosphate
Statistical analysis description:	
The analysis was based on a linear mixed model to also address the stratification factors of the randomization.	
Comparison groups	Nicotinamide v Placebo
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-0.506
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.723
upper limit	-0.289

## Secondary: Serum Phosphate (Per Protocol Population)

End point title	Serum Phosphate (Per Protocol Population)
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Nicotinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	119		
Units: mg/dL				
arithmetic mean (standard deviation)	5.25 ( $\pm$ 1.217)	5.84 ( $\pm$ 1.360)		

## Statistical analyses

Statistical analysis title	Secondary Endpoint Serum Phosphat PP Population
Comparison groups	Nicotinamide v Placebo
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.37

## Secondary: Serum Phosphate (Completer Population)

End point title	Serum Phosphate (Completer Population)
End point description:	The completers population consisted of patients who neither terminated study medication intake permanently nor study participation prematurely (i.e. before week 52) and who had a record for serum phosphate at week 52 irrespective of whether the phosphate value at screening was missing.
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Nicotinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	107		
Units: mg/dL				
arithmetic mean (standard deviation)	5.41 ( $\pm$ 1.412)	5.76 ( $\pm$ 1.513)		

## Statistical analyses

<b>Statistical analysis title</b>	Secondary Endpoint Serum Phosphat Completers Popul
Comparison groups	Placebo v Nicotinamide
Number of subjects included in analysis	358
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0309
Method	Kruskal-wallis

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Screening examination until week 52. Adverse events occurring within 4 weeks after last intake of study medication were additionally recorded.

Adverse event reporting additional description:

Adverse events were registred continuously during the clinical trial at each study visit. All adverse events were recorded irregardless wether the patient was under study medication or it was terminated.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Nicotinamide
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Nicotinamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	274 / 540 (50.74%)	93 / 183 (50.82%)	
number of deaths (all causes)	32	11	
number of deaths resulting from adverse events	32	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carcinoid tumour pulmonary			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon adenoma			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eosinophilic leukaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung carcinoma cell type unspecified stage III			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm papilla of Vater			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Air embolism			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic macroangiopathy			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic microangiopathy			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Haematoma			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	8 / 540 (1.48%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	8 / 540 (1.48%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	5 / 540 (0.93%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			



subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	14 / 540 (2.59%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 18	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein stenosis			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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			
Analgesic intervention supportive therapy			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula operation			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous shunt operation			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter removal			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheterisation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Debridement			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot amputation			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stapling			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ventilation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroidectomy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stent insertion			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polypectomy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of renal transplant			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant			
subjects affected / exposed	40 / 540 (7.41%)	17 / 183 (9.29%)	
occurrences causally related to treatment / all	0 / 40	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Resuscitation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent placement			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal fistula repair			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	3 / 540 (0.56%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	3 / 540 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Condition aggravated			
subjects affected / exposed	13 / 540 (2.41%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	3 / 14	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	3 / 540 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Device malfunction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic cyst			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Necrosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	4 / 540 (0.74%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 540 (0.74%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden cardiac death			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Sudden death			

subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Patient uncooperative			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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			
Breast inflammation			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal prolapse			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	10 / 540 (1.85%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoventilation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	7 / 540 (1.30%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	2 / 11	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	



Pulmonary congestion			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	12 / 540 (2.22%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 15	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Agitation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organic brain syndrome			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystitis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver disorder			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Antineutrophil cytoplasmic antibody positive			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram coronary			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy prostate			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood albumin abnormal			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein abnormal			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal scratch			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
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	6 / 540 (1.11%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical vertebral fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	2 / 540 (0.37%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis related complication			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	5 / 540 (0.93%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fat embolism			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodialysis complication			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation of wound			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ventilation complication			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			



subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 540 (0.19%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt aneurysm			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt stenosis			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
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	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tibia fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
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	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	4 / 540 (0.74%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 540 (0.93%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aortic valve incompetence			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	5 / 540 (0.93%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 540 (1.11%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	5 / 540 (0.93%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiac failure			
subjects affected / exposed	7 / 540 (1.30%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	7 / 540 (1.30%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	1 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	6 / 540 (1.11%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arachnoid cyst			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral circulatory failure			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clonus			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			

subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
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 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intercostal neuralgia			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			



subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	4 / 540 (0.74%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	13 / 540 (2.41%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	2 / 21	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anaemia macrocytic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 540 (0.74%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Age-related macular degeneration subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid haematoma subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain subjects affected / exposed	4 / 540 (0.74%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	2 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			

subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal erosion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bowel movement irregularity			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	4 / 540 (0.74%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal polyp			

subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enteritis			
subjects affected / exposed	0 / 540 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 540 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	7 / 540 (1.30%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	2 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal mucosa hyperaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 540 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Large intestine polyp			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 540 (0.93%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			



subjects affected / exposed	6 / 540 (1.11%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ulcer			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	3 / 540 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Calculus urethral			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism secondary			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondritis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondropathy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loose body in joint			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	6 / 540 (1.11%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthropathy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Abscess limb</b>			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Acarodermatitis</b>			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Appendicitis</b>			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Appendicitis perforated</b>			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Arteriovenous fistula site infection</b>			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bacteraemia</b>			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bacterial disease carrier</b>			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bacterial infection</b>			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	9 / 540 (1.67%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	1 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 540 (0.37%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic gangrene			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 540 (0.19%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis brain stem			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 540 (0.56%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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 / 540 (0.19%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 540 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal candidiasis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	4 / 540 (0.74%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningoencephalitis			



subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningomyelitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infected cyst			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	11 / 540 (2.04%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	4 / 540 (0.74%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Listeriosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathogen resistance			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	29 / 540 (5.37%)	8 / 183 (4.37%)	
occurrences causally related to treatment / all	0 / 29	0 / 10	
deaths causally related to treatment / all	0 / 3	0 / 3	
Pneumonia influenzal			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (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	3 / 540 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	11 / 540 (2.04%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 11	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Septic shock			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shunt infection			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 540 (0.19%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	5 / 540 (0.93%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 540 (0.37%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
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	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	5 / 540 (0.93%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Uterine infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	2 / 540 (0.37%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Metabolism and nutrition disorders</b>			
<b>Dehydration</b>			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Diabetic ketoacidosis</b>			
subjects affected / exposed	0 / 540 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Fluid overload</b>			
subjects affected / exposed	5 / 540 (0.93%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Hypercalcaemia</b>			
subjects affected / exposed	1 / 540 (0.19%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hyperkalaemia</b>			
subjects affected / exposed	1 / 540 (0.19%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hypervolaemia</b>			
subjects affected / exposed	3 / 540 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hypoglycaemia</b>			
subjects affected / exposed	1 / 540 (0.19%)	1 / 183 (0.55%)	
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 %

<b>Non-serious adverse events</b>	Nicotinamide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	511 / 540 (94.63%)	159 / 183 (86.89%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	82 / 540 (15.19%)	22 / 183 (12.02%)	
occurrences (all)	118	29	
Hypotension			
subjects affected / exposed	28 / 540 (5.19%)	12 / 183 (6.56%)	
occurrences (all)	39	16	
Surgical and medical procedures			
Renal transplant			
subjects affected / exposed	40 / 540 (7.41%)	17 / 183 (9.29%)	
occurrences (all)	40	17	
Nervous system disorders			
Headache			
subjects affected / exposed	53 / 540 (9.81%)	13 / 183 (7.10%)	
occurrences (all)	73	15	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	30 / 540 (5.56%)	8 / 183 (4.37%)	
occurrences (all)	35	9	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	60 / 540 (11.11%)	13 / 183 (7.10%)	
occurrences (all)	90	15	
Thrombocytopenia			
subjects affected / exposed	28 / 540 (5.19%)	2 / 183 (1.09%)	
occurrences (all)	39	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	240 / 540 (44.44%)	51 / 183 (27.87%)	
occurrences (all)	451	71	
Nausea			

subjects affected / exposed	79 / 540 (14.63%)	20 / 183 (10.93%)	
occurrences (all)	104	27	
Vomiting			
subjects affected / exposed	62 / 540 (11.48%)	10 / 183 (5.46%)	
occurrences (all)	79	16	
Abdominal pain			
subjects affected / exposed	23 / 540 (4.26%)	11 / 183 (6.01%)	
occurrences (all)	26	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 540 (7.59%)	9 / 183 (4.92%)	
occurrences (all)	53	10	
Dyspnoea			
subjects affected / exposed	30 / 540 (5.56%)	4 / 183 (2.19%)	
occurrences (all)	41	6	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	74 / 540 (13.70%)	12 / 183 (6.56%)	
occurrences (all)	97	12	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	32 / 540 (5.93%)	9 / 183 (4.92%)	
occurrences (all)	39	9	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	48 / 540 (8.89%)	18 / 183 (9.84%)	
occurrences (all)	82	43	
Arthralgia			
subjects affected / exposed	23 / 540 (4.26%)	13 / 183 (7.10%)	
occurrences (all)	26	15	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	97 / 540 (17.96%)	26 / 183 (14.21%)	
occurrences (all)	133	41	
Bronchitis			



subjects affected / exposed	55 / 540 (10.19%)	13 / 183 (7.10%)	
occurrences (all)	66	17	
Pneumonia			
subjects affected / exposed	35 / 540 (6.48%)	9 / 183 (4.92%)	
occurrences (all)	37	11	
Urinary tract infection			
subjects affected / exposed	29 / 540 (5.37%)	8 / 183 (4.37%)	
occurrences (all)	34	8	
Herpes zoster			
subjects affected / exposed	29 / 540 (5.37%)	0 / 183 (0.00%)	
occurrences (all)	31	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	36 / 540 (6.67%)	10 / 183 (5.46%)	
occurrences (all)	46	10	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2013	Change in Prohibited Comedications: Magnesium intake should be generally allowed.
22 December 2013	Change in inclusion and exclusion criteria: Inclusionrange of phosphate concentration was extendet to < 2.42 mmol/l (7.5 mg/dl) and > 1.45 mmol/l (4.5 mg/dl). Intake of concomitent medication nicontic acid was allowed up to a dose of 150 mg / week.
10 June 2014	Change in inclusion and exclusion criteria: Permission of a second phosphat binder. Inclusionrange of phosphate concentration was extendet to < 2.80 mmol/l (8.7 mg/dl) and > 1.45 mmol/l (4.5 mg/dl).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported