Clinical trial results:
A multicenter, randomized, placebo-controlled, double-blind study on the efficacy, safety and tolerability of Certican® in preventing end-stage renal disease (ESRD) in patients with autosomal dominant polycystic kidney disease (ADPKD)

Summary

EudraCT number	2006-001485-16
Trial protocol	AT DE FR
Global end of trial date	11 October 2013

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001ADE12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00414440
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2013
Global end of trial reached?	Yes
Global end of trial date	11 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to demonstrate that everolimus has superior efficacy compared with placebo in reducing the mean total kidney volume from baseline to 24 months of treatment in patients with ADPKD.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 371
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Austria: 25
Worldwide total number of subjects	431
EEA total number of subjects	431

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	423

From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

431 patients were randomized to the two treatment groups in a 1:1 ratio

Period 1

Period 1 title	Core period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus

Arm description:

Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).

Arm title	Placebo

Arm description:

Placebo tablets equivalent to the dosage of everolimus 5 mg/day, divided in 2 equal doses.

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).

Number of subjects in period 1	Everolimus	Placebo
Started	214	217
Completed	144	185
Not completed	70	32
Consent withdrawn by subject	70	32

Period 2

Period 2 title	Extension period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus

Arm description:

Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).

Arm title	Placebo

Arm description:

Placebo tablets equivalent to the dosage of everolimus 5 mg/day, divided in 2 equal doses.

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).

Number of subjects in period 2	Everolimus	Placebo
Started	144	185
Completed	73	107
Not completed	71	78
Adverse event, serious fatal	1	2
Consent withdrawn by subject	9	7
Administrative	16	16
Unknown	1	1
Lost to follow-up	44	52

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets equivalent to the dosage of everolimus 5 mg/day, divided in 2 equal doses.	

Reporting group values	Everolimus	Placebo	Total
Number of subjects	214	217	431
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	212	215	427
From 65-84 years	2	2	4
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	44.6	44.5	
standard deviation	± 10.1	± 10.4	-
Gender, Male/Female Units: participants			
Female	105	117	222
Male	109	100	209
Race/Ethnicity, Customized Units: Subjects			
Asian Oriental	4	0	4
Black or African American	1	0	1
White	208	217	425
Other, Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Everolimus
Reporting group description:	
Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets equivalent to the dosage of everolimus 5 mg/day, divided in 2 equal doses.	
Reporting group title	Everolimus
Reporting group description:	
Patients in the everolimus group initially received 5 mg/day everolimus divided in 2 equal doses (i.e. 2.5 mg b.i.d.). Dose adjustments were performed to achieve a blood trough level of 3-8 ng/mL (maximum daily dose: 10 mg/day [5 mg b.i.d.]).	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets equivalent to the dosage of everolimus 5 mg/day, divided in 2 equal doses.	

Primary: Primary efficacy analysis of total kidney volume (mITT set, multiple imputation)

End point title	Primary efficacy analysis of total kidney volume (mITT set, multiple imputation)
End point description:	
Everolimus (RAD001) compared to placebo with respect to the change from baseline in total kidney volume at Month 24.	
End point type	Primary
End point timeframe:	
Baseline, Month 24	

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	217		
Units: mL				
arithmetic mean (confidence interval)	230.1 (172.4 to 287.9)	300.8 (247.5 to 354.1)		

Statistical analyses

Statistical analysis title	Analysis of Kidney Volume (mITT set)
Comparison groups	Everolimus v Placebo

Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.062
Method	ANCOVA

Secondary: Course of calculated GFR (mL/min/1.73 m^2) from Month 24 to Month 60

End point title	Course of calculated GFR (mL/min/1.73 m^2) from Month 24 to Month 60

End point description:

Course of calculated GFR (mL/min/1.73 m^2) at Months 24, 36, 48 and 60

End point type	Secondary

End point timeframe:

Months 24, 36, 48 and 60

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	217		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Month 24	43.9 (± 23.9)	48.8 (± 20.8)		
Month 36	42.6 (± 23.5)	44.9 (± 22.2)		
Month 48	39.6 (± 22.2)	42.7 (± 22.5)		
Month 60	37.7 (± 23.8)	37.6 (± 21.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated GFR, change from baseline at Month 60 by baseline cGFR

End point title	Calculated GFR, change from baseline at Month 60 by baseline cGFR

End point description:

Change in renal function was assessed by the estimated Glomerular Filtration Rate (eGFR) using the abbreviated (4 variables) Modification of Diet in Renal Disease (MDRD-4) formula which was developed by the MDRD Study Group and has been validated in patients with chronic kidney disease. The MDRD-4 formula used for the eGFR calculation is: eGFR (mL/min/1.73m^2) = 186.3*(C^-1.154)*(A^-0.203)*G*R, where C is the serum concentration of creatinine (mg/dL), A is age (years), G=0.742 when gender is female, otherwise G=1, R=1.21 when race is black, otherwise R=1. The changes in renal function were analyzed via analysis of covariance (ANCOVA) with treatment, pre-transplant hepatitis C virus status and randomization eGFR as covariates. Based on these ANCOVA analyses, the least-squares mean and standard errors of change were reported.

End point type	Secondary

End point timeframe:

Months 24, 36, 48 and 60

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	75		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
>70 mL/min/1.73 m^2 n=11, 18	-14.8 (± 22.7)	-20.5 (± 11.1)		
≤70 mL/min/1.73 m^2 n=53, 57	-16.1 (± 17.6)	-15.6 (± 15.2)		
>60 mL/min/1.73 m^2 n=21.26	-17 (± 17.3)	-20 (± 13.6)		
≤60 mL/min/1.73 m^2 n=43,49	-15.3 (± 19)	-15.1 (± 14.7)		
>50 mL/min/1.73 m^2 n=36,39	-19 (± 17.3)	-19.4 (± 12.6)		
≤50 mL/min/1.73 m^2 n=28, 36	-11.8 (± 19.2)	-14 (± 15.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point title	Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point description:

Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), at baseline and then months 12 and 24

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	216		
Units: mmHG				
arithmetic mean (standard deviation)				
Baseline SBP	136 (± 16)	135 (± 17)		
Month 12 SBP	134 (± 15)	134 (± 16)		
Month 24 SBP	134 (± 17)	134 (± 15)		
Baseline DBP	88 (± 11)	88 (± 10)		
Month 12 DBP	86 (± 10)	86 (± 10)		
Month 24 DBP	85 (± 10)	85 (± 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated GFR (mL/min/1.73 m^2), change from baseline by visit

End point title	Calculated GFR (mL/min/1.73 m^2), change from baseline by visit

End point description:

Change in renal function was assessed by the Glomerular Filtration Rate (GFR) using the abbreviated (4 variables) Modification of Diet in Renal Disease (MDRD-4) formula which was developed by the MDRD Study Group and has been validated in patients with chronic kidney disease. The MDRD-4 formula used for the eGFR calculation is: eGFR (mL/min/1.73m^2) = 186.3*(C^-1.154)*(A^-0.203)*G*R, where C is the serum concentration of creatinine (mg/dL), A is age (years), G=0.742 when gender is female, otherwise G=1, R=1.21 when race is black, otherwise R=1. The changes in renal function were analyzed via analysis of covariance (ANCOVA) with treatment, pre-transplant hepatitis C virus status and randomization eGFR as covariates. Based on these ANCOVA analyses, the least-squares mean and standard errors of change were reported.

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12, 18 and 24

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	216		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)				
Week 1	2 (± 5.9)	-0.9 (± 6.1)		
Week 2	1.7 (± 5.9)	-0.9 (± 6.5)		
Week 4	0.6 (± 6.3)	-1.2 (± 6.7)		
Month 3	-0.5 (± 8.2)	-2.4 (± 6.7)		
Month 6	-2.3 (± 7.7)	-2.2 (± 6.7)		
Month 9	-4.6 (± 8.2)	-2.4 (± 6)		
Month 12	-5.4 (± 7.5)	-3.2 (± 6.9)		
Month 18	-7.7 (± 8.5)	-5.5 (± 6.7)		
Month 24	-8.9 (± 8.8)	-7.7 (± 6.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Everolimus	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 214 (37.38%)	51 / 217 (23.50%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ovarian tumour			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 214 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery stenosis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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			
Asthenia			
subjects affected / exposed	2 / 214 (0.93%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bloody discharge			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	4 / 214 (1.87%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema peripheral			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
House dust allergy			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast discharge			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast fibrosis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast hyperplasia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colpocele			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysmenorrhoea			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menstruation irregular			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fluid collection			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	7 / 214 (3.27%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycystic ovaries			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			

subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Painful respiration			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute psychosis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	3 / 214 (1.40%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	4 / 214 (1.87%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal abrasion			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Conjunctival abrasion			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in eye			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 214 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
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 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
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			

Polycystic liver disease			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	0 / 214 (0.00%)	3 / 217 (1.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopericarditis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral atrophy			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 214 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node pain			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute vestibular syndrome			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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 pain			
subjects affected / exposed	2 / 214 (0.93%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	2 / 214 (0.93%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal tenderness			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic polyp			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 214 (1.40%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 214 (0.93%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	3 / 214 (1.40%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst ruptured			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	8 / 214 (3.74%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia facial			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 214 (0.93%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	5 / 214 (2.34%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haemorrhage			

subjects affected / exposed	3 / 214 (1.40%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 214 (0.93%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	2 / 214 (0.93%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	4 / 214 (1.87%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anogenital warts			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (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	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 214 (1.40%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster ophthalmic			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			

subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma viral infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 214 (2.34%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 214 (0.47%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	2 / 214 (0.93%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 214 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 214 (0.47%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	2 / 214 (0.93%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	205 / 214 (95.79%)	185 / 217 (85.25%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	38 / 214 (17.76%)	13 / 217 (5.99%)	
occurrences (all)	39	15	
Blood creatine phosphokinase increased			
subjects affected / exposed	32 / 214 (14.95%)	15 / 217 (6.91%)	
occurrences (all)	39	16	
Vascular disorders			
Hypertension			
subjects affected / exposed	33 / 214 (15.42%)	29 / 217 (13.36%)	
occurrences (all)	35	30	
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 214 (17.29%)	27 / 217 (12.44%)	
occurrences (all)	49	45	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	35 / 214 (16.36%)	11 / 217 (5.07%)	
occurrences (all)	35	11	
Thrombocytopenia			
subjects affected / exposed	30 / 214 (14.02%)	2 / 217 (0.92%)	
occurrences (all)	32	2	
Leukopenia			
subjects affected / exposed	38 / 214 (17.76%)	6 / 217 (2.76%)	
occurrences (all)	42	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 214 (5.14%)	6 / 217 (2.76%)	
occurrences (all)	12	7	
Oedema			
subjects affected / exposed	25 / 214 (11.68%)	12 / 217 (5.53%)	
occurrences (all)	27	13	
Oedema peripheral			

subjects affected / exposed	42 / 214 (19.63%)	20 / 217 (9.22%)	
occurrences (all)	47	23	
Pyrexia			
subjects affected / exposed	12 / 214 (5.61%)	9 / 217 (4.15%)	
occurrences (all)	13	9	
Fatigue			
subjects affected / exposed	20 / 214 (9.35%)	19 / 217 (8.76%)	
occurrences (all)	21	21	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	12 / 214 (5.61%)	8 / 217 (3.69%)	
occurrences (all)	14	8	
Abdominal pain			
subjects affected / exposed	24 / 214 (11.21%)	13 / 217 (5.99%)	
occurrences (all)	26	13	
Abdominal pain upper			
subjects affected / exposed	14 / 214 (6.54%)	13 / 217 (5.99%)	
occurrences (all)	16	14	
Aphthous stomatitis			
subjects affected / exposed	83 / 214 (38.79%)	12 / 217 (5.53%)	
occurrences (all)	121	14	
Vomiting			
subjects affected / exposed	11 / 214 (5.14%)	14 / 217 (6.45%)	
occurrences (all)	11	14	
Nausea			
subjects affected / exposed	20 / 214 (9.35%)	12 / 217 (5.53%)	
occurrences (all)	21	13	
Diarrhoea			
subjects affected / exposed	48 / 214 (22.43%)	34 / 217 (15.67%)	
occurrences (all)	58	35	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 214 (11.21%)	19 / 217 (8.76%)	
occurrences (all)	31	20	
Oropharyngeal pain			

subjects affected / exposed	12 / 214 (5.61%)	9 / 217 (4.15%)	
occurrences (all)	15	11	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	30 / 214 (14.02%)	6 / 217 (2.76%)	
occurrences (all)	34	7	
Rash			
subjects affected / exposed	18 / 214 (8.41%)	8 / 217 (3.69%)	
occurrences (all)	18	10	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	28 / 214 (13.08%)	15 / 217 (6.91%)	
occurrences (all)	28	15	
Haematuria			
subjects affected / exposed	13 / 214 (6.07%)	9 / 217 (4.15%)	
occurrences (all)	19	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 214 (6.07%)	5 / 217 (2.30%)	
occurrences (all)	17	6	
Back pain			
subjects affected / exposed	15 / 214 (7.01%)	17 / 217 (7.83%)	
occurrences (all)	16	21	
Flank pain			
subjects affected / exposed	17 / 214 (7.94%)	23 / 217 (10.60%)	
occurrences (all)	20	25	
Muscle spasms			
subjects affected / exposed	10 / 214 (4.67%)	12 / 217 (5.53%)	
occurrences (all)	11	13	
Myalgia			
subjects affected / exposed	14 / 214 (6.54%)	3 / 217 (1.38%)	
occurrences (all)	16	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 214 (9.81%)	23 / 217 (10.60%)	
occurrences (all)	23	26	

Gastroenteritis			
subjects affected / exposed	11 / 214 (5.14%)	4 / 217 (1.84%)	
occurrences (all)	12	4	
Nasopharyngitis			
subjects affected / exposed	83 / 214 (38.79%)	83 / 217 (38.25%)	
occurrences (all)	123	124	
Oral herpes			
subjects affected / exposed	15 / 214 (7.01%)	4 / 217 (1.84%)	
occurrences (all)	16	4	
Sinusitis			
subjects affected / exposed	14 / 214 (6.54%)	13 / 217 (5.99%)	
occurrences (all)	15	14	
Urinary tract infection			
subjects affected / exposed	22 / 214 (10.28%)	19 / 217 (8.76%)	
occurrences (all)	27	31	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	46 / 214 (21.50%)	8 / 217 (3.69%)	
occurrences (all)	47	9	
Hyperlipidaemia			
subjects affected / exposed	28 / 214 (13.08%)	5 / 217 (2.30%)	
occurrences (all)	28	5	
Hypertriglyceridaemia			
subjects affected / exposed	15 / 214 (7.01%)	8 / 217 (3.69%)	
occurrences (all)	15	8	
Hyperuricaemia			
subjects affected / exposed	7 / 214 (3.27%)	13 / 217 (5.99%)	
occurrences (all)	7	14	
Iron deficiency			
subjects affected / exposed	12 / 214 (5.61%)	2 / 217 (0.92%)	
occurrences (all)	12	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2007	Issued approximately 9 months after study start / after randomization of 339 patients was to: -recalculate the required sample size (increase by 50 patients per group) to compensate for the drop-out rate which had been underestimated and to provide measures to maintain sufficient power in case of increased standard deviations - clarify the wording with respect to the primary variable, and to correct the alpha levels to be chosen for the statistical hypothesis, model, and method of analysis, which had been given erroneously in the study protocol from a draft version but not the final planning -introduce a multiple imputation procedure for dealing with missing values during analysis
09 March 2012	Issued approximately 36 months after completion of the core study was to: - extend the observation period of all patients for another 12 months to a total of 60 months - introduce an exploratory genome-wide analysis of each individual patient by applying e.g. Next-Generation Sequencing. The necessary DNA sample and informed consent were to be obtained during the additional visit at Month 60.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported