Clinical trial results:
A randomized, double-blind, multicenter, Phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin - RADIANT-4

Summary

EudraCT number	2011-002887-26
Trial protocol	BE AT DE CZ HU ES GB IT NO NL GR SK PL
Global end of trial date	07 August 2020

Results information

Result version number	v1 (current)
This version publication date	29 July 2021
First version publication date	29 July 2021

Trial information

Trial identification

Sponsor protocol code	CRAD001T2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01524783
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether treatment with everolimus 10 mg daily plus best supportive care prolongs progression-free survival compared with placebo plus best supportive care in patients with advanced neuroendocrine tumor (NET) of gastrointestinal (GI) or lung origin without a history of, or current symptoms of carcinoid syndrome

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	30 March 2012
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	Austria: 9
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 66
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 12
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Slovakia: 2

Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 58
Worldwide total number of subjects	302
EEA total number of subjects	145

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)	159
From 65 to 84 years	141
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

As per Data Monitoring Committee recommendation (03-Jun-2015), implemented through protocol amendment 3 (issued on 06-May-2016), remaining participants entered the open-label part of the study, where participants in the placebo arm were allowed to crossover to open-label treatment with everolimus

Pre-assignment

Screening details:

At baseline, participants were randomized to either everolimus+BSC or placebo+BSC arm. Two patients randomized to the everolimus arm were not treated due to withdrawal of consent and protocol deviation.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus + BSC

Arm description:

Participants received everolimus 10 mg once daily BSC throughout the study

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:

Everolimus 10 mg (two 5 mg tablets) once daily orally taken

Arm title	Placebo+BSC

Arm description:

Participants received matching placebo once daily plus best supportive care (BSC) during the blinded period. Participants were allowed to crossover to treatment with everolimus 10mg once daily plus BSC during the open-label period

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

Dosage and administration details:

Two tablets of matching placebo once daily orally taken.

Number of subjects in period 1	Everolimus + BSC	Placebo+BSC
Started	205	97
Completed	26	6
Not completed	179	91
Adverse event, serious fatal	5	2
Consent withdrawn by subject	19	6
Adverse event, non-fatal	64	7
Protocol deviation	2	1
Disease Progression	89	75

Period 2

Period 2 title	Open-label period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus + BSC

Arm description:

Participants received everolimus 10 mg once daily plus best supportive care (BSC) throughout the study

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:

Everolimus 10 mg (two 5 mg tablets) once daily orally taken

Arm title	Everolimus +BSC (crossover)

Arm description:

Participants who crossed over from placebo arm (blinded period) to open-label treatment with everolimus 10mg once daily plus BSC

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:

Everolimus 10 mg (two 5 mg tablets) once daily orally taken

Number of subjects in period 2	Everolimus + BSC	Everolimus +BSC (crossover)
Started	26	6
Completed	0	0
Not completed	26	6
Consent withdrawn by subject	2	1
Adverse event, non-fatal	5	1
Protocol deviation	1	-
Administrative problems	5	2
Disease Progression	13	2

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus + BSC
Reporting group description:	
Participants received everolimus 10 mg once daily BSC throughout the study	
Reporting group title	Placebo+BSC
Reporting group description:	
Participants received matching placebo once daily plus best supportive care (BSC) during the blinded period. Participants were allowed to crossover to treatment with everolimus 10mg once daily plus BSC during the open-label period	

Reporting group values	Everolimus + BSC	Placebo+BSC	Total
Number of subjects	205	97	302
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)	100	59	159
From 65-84 years	103	38	141
85 years and over	2	0	2
Age Continuous			
Age continuous at Baseline: Blinded Period			
Units: years			
arithmetic mean	62.9	59.4	
standard deviation	± 11.70	± 12.89	-
Sex: Female, Male			
Gender at Baseline: Blinded period			
Units: Participants			
Female	116	44	160
Male	89	53	142
Race/Ethnicity, Customized			
Race at Baseline: Blinded-period			
Units: Subjects			
Caucasian	162	68	230
Asian	32	18	50
Black	6	9	15
Other	5	2	7

End points

End points reporting groups

Reporting group title	Everolimus + BSC
Reporting group description:	
Participants received everolimus 10 mg once daily BSC throughout the study	
Reporting group title	Placebo+BSC
Reporting group description:	
Participants received matching placebo once daily plus best supportive care (BSC) during the blinded period. Participants were allowed to crossover to treatment with everolimus 10mg once daily plus BSC during the open-label period	
Reporting group title	Everolimus + BSC
Reporting group description:	
Participants received everolimus 10 mg once daily plus best supportive care (BSC) throughout the study	
Reporting group title	Everolimus +BSC (crossover)
Reporting group description:	
Participants who crossed over from placebo arm (blinded period) to open-label treatment with everolimus 10mg once daily plus BSC	
Subject analysis set title	Everolimus+BSC (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least one dose of everolimus and had at least one post-baseline safety evaluation. Patients were analyzed according to treatment actually received.	
Subject analysis set title	Everolimus +BSC (crossover) (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who crossed over from placebo to open-label treatment with everolimus and received at least one dose of everolimus and had at least one post-baseline safety evaluation. Patients were analyzed according to treatment actually received.	
Subject analysis set title	Everolimus+BSC (all) (Safety set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received everolimus 10 mg once daily plus BSC (including those who received everolimus+BSC from start to end of the study and those who received everolimus+BSC after crossover)	
Subject analysis set title	Placebo+BSC (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least one dose of placebo and had at least one post-baseline safety evaluation. Patients were analyzed according to treatment actually received.	

Primary: Probability of Participants Remaining Event-Free in Progression-Free Survival (PFS) based on central radiology assessment

End point title	Probability of Participants Remaining Event-Free in Progression-Free Survival (PFS) based on central radiology assessment

End point description:

PFS is defined as the time from randomization to the date of the first documented tumor progression or death from any cause, whichever comes first.
Progression was defined using modified RECIST 1.0 and as per central radiology assessment as at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. Progression was assessed by cat scan and/or magnetic resonance imaging.
For participants who had not progressed or died at the analysis cut-off date, PFS was censored at the date of the last adequate tumor evaluation date. An adequate tumour assessment is a tumour assessment with an overall response other than unknown.
The percentage event-free probability estimate is the estimated probability that a patient will remain

event-free in PFS up to the specified time point.
Note: 999 indicates value is not estimable

End point type	Primary

End point timeframe:

From date of randomization to progression or death, whichever comes first, assessed up to 27 months

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: Percent event-free probability in PFS				
number (confidence interval 95%)				
2 months	90.1 (84.8 to 93.5)	74.6 (64.3 to 82.4)		
4 months	81.2 (74.9 to 86.2)	49.1 (38.1 to 59.2)		
6 months	72.1 (65.0 to 78.0)	40.1 (29.5 to 50.5)		
8 months	62.4 (54.8 to 69.1)	35.8 (25.4 to 46.2)		
10 months	51.7 (44.0 to 59.0)	31.3 (21.3 to 41.7)		
12 months	44.4 (36.7 to 51.8)	28.1 (18.5 to 38.6)		
15 months	40.1 (32.5 to 47.6)	26.4 (16.9 to 36.8)		
18 months	31.8 (24.1 to 39.8)	24.4 (15.0 to 34.9)		
21 months	27.6 (19.0 to 36.8)	17.4 (9.0 to 28.2)		
24 months	22.0 (13.0 to 32.5)	17.4 (9.0 to 28.2)		
27 months	999 (999 to 999)	17.4 (9.0 to 28.2)		

Statistical analyses

Statistical analysis title	Everolimus vs Placebo
Comparison groups	Everolimus + BSC v Placebo+BSC
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.67

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from the date of randomization to date of death due to any cause. If a death had not been observed by the date of analysis cut-off, then OS was censored at the date of last contact. All participants randomized to placebo arm who crossed over to everolimus were censored.

End point type	Secondary

End point timeframe:

From date of randomization to date of death, assessed up to approximately 8 years

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: Months				
median (confidence interval 95%)	43.1 (36.27 to 54.24)	41.76 (23.46 to 53.75)		

Statistical analyses

Statistical analysis title	Everolimus vs Placebo
Comparison groups	Everolimus + BSC v Placebo+BSC
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.24

Secondary: Overall response rate (ORR) as per modified RECIST 1.0 according to central evaluation

End point title	Overall response rate (ORR) as per modified RECIST 1.0 according to central evaluation

End point description:

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), according to central evaluation and as per modified RECIST 1.0.
CR: disappearance of all target lesions.
PR: At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.

End point type	Secondary

End point timeframe:

From randomization until end of treatment, assessed up to approximately 2.5 years

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: Percentage of participants				
number (confidence interval 95%)	2.0 (0.5 to 4.9)	1.0 (0.0 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) based on modified RECIST 1.0 and as per central radiology assessment

End point title	Disease control rate (DCR) based on modified RECIST 1.0 and as per central radiology assessment

End point description:

DCR is defined as the proportion of subjects with best overall response of CR or PR or stable disease based on modified RECIST 1.0 and as per central radiology assessment.
CR: disappearance of all target lesions.
PR: At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.
Stable disease: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.

End point type	Secondary

End point timeframe:

From randomization until end of treatment, assessed up to approximately 2.5 years

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: Percentage of participants				
number (confidence interval 95%)	82.4 (76.5 to 87.4)	64.9 (54.6 to 74.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration in Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire total score

End point title	Time to definitive deterioration in Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire total score

End point description:

FACT-G is a self-assessed health-related quality of life questionnaire. The questionnaire is comprised of 27 questions examining physical, social/family, emotional, and functional well-being. Participants responded to the items on a five-point scale, ranging from 0: "Not at all" to 4: "Very much." The total score ranges from 0 to 108, with higher scores indicating a better patient-reported outcome/quality of life.
Definitive deterioration is defined as a decrease in the total score by at least 7 points compared to baseline with no further improvement.
Death was considered as worsening of the FACT-G total score if it occurred close to the last available assessment, where “close” was defined as twice the planned period between two assessments. Patients without definitive worsening prior to analysis cut-off or prior to start of another anticancer therapy were censored at the date of their last assessment.

End point type	Secondary

End point timeframe:

From randomization to definitive deterioration of FACT-G total score, assessed up to approximately 3 years

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: Months				
median (confidence interval 95%)	13.01 (9.33 to 24.80)	9.23 (5.52 to 28.62)		

Statistical analyses

Statistical analysis title	Everolimus vs Placebo
Comparison groups	Everolimus + BSC v Placebo+BSC
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.1

Secondary: Change from baseline in Chromogranin A (CgA) levels

End point title	Change from baseline in Chromogranin A (CgA) levels

End point description:

CgA is a potential biomarker for tumor response. Blood samples were collected for assessment of CgA levels. Change from Baseline at a particular visit was calculated as the CgA level at that visit minus Baseline.
Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

End point type	Secondary

End point timeframe:

From baseline (every 4 weeks) up to 116 weeks

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: microgram/liter (ug/L)				
arithmetic mean (standard deviation)				
Week 4 (n= 164 / 90)	434.8 (± 2306.70)	1154.3 (± 9083.39)		
Week 8 (n= 156 / 88)	162.3 (± 2550.65)	2697.6 (± 19956.90)		
Week 12 (n= 143 / 75)	396.7 (± 2401.78)	1176.0 (± 3322.13)		
Week 16 (n= 141 / 62)	263.5 (± 2946.76)	1450.4 (± 4825.78)		
Week 20 (n= 131/ 51)	162.1 (± 2464.47)	3640.1 (± 12653.42)		
Week 24 (n= 119 / 39)	253.2 (± 3487.27)	1783.9 (± 5399.98)		
Week 28 (n= 112/ 35)	587.2 (± 4861.35)	1350.3 (± 5701.70)		
Week 32 (n= 109 / 31)	508.5 (± 6102.61)	2000.7 (± 6362.83)		
Week 36 (n= 97 / 26)	94.7 (± 4905.17)	180.9 (± 383.93)		
Week 40 (n= 87 / 24)	511.4 (± 6180.67)	207.6 (± 403.30)		
Week 44 (n= 86 / 23)	552.8 (± 4173.44)	140.6 (± 328.02)		
Week 48 (n= 77 / 23)	1326.2 (± 8718.92)	129.0 (± 326.69)		
Week 52 (n= 70 / 24)	1196.2 (± 7737.76)	124.2 (± 452.38)		
Week 56 (n= 60 / 21)	1920.6 (± 11250.07)	134.9 (± 346.33)		

Week 60 (n= 60 / 19)	1722.0 (± 13155.03)	120.9 (± 415.73)		
Week 64 (n= 59 / 19)	3811.0 (± 26656.45)	141.6 (± 281.38)		
Week 68 (n= 56 / 17)	1413.3 (± 9588.68)	222.6 (± 333.93)		
Week 72 (n= 53 / 17)	239.5 (± 2318.79)	233.7 (± 400.43)		
Week 76 (n= 51 / 16)	3256.5 (± 19395.40)	210.9 (± 522.62)		
Week 80 (n= 49 / 15)	5421.0 (± 32471.22)	286.3 (± 425.45)		
Week 84 (n= 45 / 14)	4379.9 (± 28302.84)	175.4 (± 575.98)		
Week 88 (n= 36 / 11)	571.2 (± 2694.44)	-9.4 (± 473.66)		
Week 92 (n= 30 / 10)	765.5 (± 2913.15)	63.7 (± 477.53)		
Week 96 (n= 24 / 10)	984.6 (± 3379.28)	146.5 (± 468.24)		
Week 100 (n= 22 / 6)	935.3 (± 2961.60)	-12.7 (± 399.25)		
Week 104 (n= 15 / 6)	1466.4 (± 4257.03)	-21.7 (± 285.99)		
Week 108 (n= 12 / 6)	2245.8 (± 6077.99)	215.9 (± 293.87)		
Week 112 (n= 12 / 4)	2817.0 (± 7786.28)	514.5 (± 661.80)		
Week 116 (n= 6 / 4)	2951.8 (± 6745.06)	99.6 (± 92.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Neuron specific enolase (NSE) levels

End point title	Change from baseline in Neuron specific enolase (NSE) levels

End point description:

NSE is a potential biomarker for tumor response. Blood samples were collected for assessment of NSE levels. Change from Baseline at a particular visit was calculated as the NSE level at that visit minus Baseline.
Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

End point type	Secondary

End point timeframe:

From baseline (every 4 weeks) up to Week 116

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: microgram/liter (ug/L)				
arithmetic mean (standard deviation)				
Week 4 (n= 158 / 89)	0.1 (± 5.21)	-2.2 (± 39.87)		
Week 8 (n= 151 / 85)	0.3 (± 8.71)	-4.2 (± 36.71)		
Week 12 (n= 139 / 74)	-0.3 (± 8.37)	15.5 (± 163.75)		
Week 16 (n= 135 / 62)	2.0 (± 8.34)	4.1 (± 19.44)		
Week 20 (n= 128 / 50)	0.8 (± 6.21)	5.3 (± 18.26)		
Week 24 (n= 117 / 39)	1.7 (± 8.99)	6.7 (± 23.47)		
Week 28 (n= 110 / 35)	1.1 (± 6.37)	0.4 (± 9.16)		
Week 32 (n= 106 / 31)	1.5 (± 14.24)	3.1 (± 8.96)		
Week 36 (n= 96 / 27)	2.0 (± 15.11)	2.0 (± 5.90)		
Week 40 (n= 86/ 24)	1.2 (± 6.48)	1.2 (± 4.49)		
Week 44 (n= 87 / 23)	0.8 (± 5.10)	1.2 (± 4.46)		
Week 48 (n= 74 / 23)	2.0 (± 9.20)	0.6 (± 4.06)		
Week 52 (n= 71 / 23)	1.5 (± 5.82)	0.7 (± 4.19)		
Week 56 (n= 60 / 21)	3.6 (± 18.56)	0.9 (± 5.89)		
Week 60 (n= 63 / 20)	2.4 (± 8.19)	0.1 (± 3.35)		
Week 64 (n= 58 / 18)	4.4 (± 23.22)	0.9 (± 3.80)		
Week 68 (n= 58 / 18)	1.1 (± 4.68)	1.9 (± 4.48)		
Week 72 (n= 53 / 18)	1.6 (± 4.46)	0.7 (± 3.91)		
Week 76 (n= 52 / 16)	1.7 (± 5.11)	0.6 (± 3.89)		
Week 80 (n= 51 / 13)	2.9 (± 10.15)	0.7 (± 2.83)		
Week 84 (n= 41 / 14)	8.0 (± 33.13)	0.1 (± 3.47)		
Week 88 (n= 37 / 11)	2.2 (± 3.89)	0.6 (± 2.47)		
Week 92 (n= 29 / 10)	4.0 (± 7.24)	0.1 (± 3.79)		
Week 96 (n= 23 / 10)	4.3 (± 5.96)	0.0 (± 2.99)		
Week 100 (n= 22 / 5)	1.8 (± 3.79)	-0.2 (± 5.10)		
Week 104 (n= 15 / 6)	2.9 (± 4.11)	-1.7 (± 4.76)		
Week 108 (n= 12 / 6)	5.5 (± 13.48)	-0.5 (± 4.33)		
Week 112 (n= 11 / 3)	2.8 (± 5.72)	-3.2 (± 3.30)		
Week 116 (n= 6 / 4)	10.6 (± 14.92)	0.2 (± 4.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration in World Health Organization (WHO) Performance Status (PS) change

End point title	Time to definitive deterioration in World Health Organization (WHO) Performance Status (PS) change

End point description:

WHO PS is a scale rated from 0 (fully active) to 5 (death) by a healthcare professional to assess the overall status of a patient: a lower score represents a higher ability to perform daily tasks. Deterioration is defined as an increase of at least one point compared to baseline. Deterioration is considered definitive if no improvements in the WHO PS status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.
Death was considered as worsening of the WHO PS if it occurred close to the last available assessment,

where “close” was defined as twice the planned period between two assessments. Patients without definitive worsening prior to analysis cut-off or prior to start of another anticancer therapy were censored at the date of their last assessment.
Note: 999 indicates value is not estimable

End point type	Secondary

End point timeframe:

From randomization to definitive deterioration of WHO performance status, assessed up to approximately 3 years

End point values	Everolimus + BSC	Placebo+BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	97		
Units: Months				
median (confidence interval 95%)	24.08 (17.05 to 999)	24.15 (8.31 to 999)		

Statistical analyses

Statistical analysis title	Everolimus vs Placebo
Comparison groups	Everolimus + BSC v Placebo+BSC
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.539
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.61

Secondary: Pharmacokinetics (PK): Predose concentration (Cmin) of everolimus at Day 29

End point title	Pharmacokinetics (PK): Predose concentration (Cmin) of everolimus at Day 29[1]

End point description:

A pre-dose blood sample at day 29 was collected to determine the exposure of everolimus at the steady-state pre-dose concentration (Cmin). Cmin is provided for participants randomized to everolimus+BSC who received 10mg of everolimus daily and also for participants randomized to everolimus+BSC who received 5mg of everolimus daily which was required for a number of participants in the study experiencing adverse events requiring dose modifications

End point type	Secondary

End point timeframe:

Pre-dose at Day 29.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for one of the arms in the baseline period

End point values	Everolimus + BSC			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
10mg daily dose	16.382 (± 13.2767)			
5mg daily dose	4.700 (± 3.8396)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

Deaths on-treatment were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approximately 8 years.
Total Deaths were collected from first dose of study treatment until end of post-treatment survival follow, up to maximum duration of approximately 8 years.
Participants were analyzed according to treatment actually received: One participant randomized to everolimus arm received only placebo and therefore, appears in the placebo arm in the safety set.

End point type	Post-hoc

End point timeframe:

On-treatment deaths: up to approximately 8 years. All deaths: up to approximately 8 years

End point values	Everolimus+BSC (Safety Set)	Everolimus +BSC (crossover) (Safety Set)	Everolimus+BSC (all) (Safety set)	Placebo+BSC (Safety Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	202	6	208	98
Units: Participants				
On-treatment deaths	10	0	10	5
Total deaths	126	1	127	57

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from date of first dose of study treatment until end of study treatment plus 30 days post treatment, assessed up to a maximum duration of approximately 8 years.

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	23.0.

Reporting groups

Reporting group title	Everolimus+BSC (throughout study)

Reporting group description:

Participants received everolimus 10 mg once daily BSC throughout the study

Reporting group title	Everolimus+BSC (crossover)

Reporting group description:

Participants who crossed over from placebo arm (blinded period) to open-label treatment with everolimus 10mg once daily plus BSC

Reporting group title	Everolimus+BSC (all)

Reporting group description:

All participants who received everolimus 10 mg once daily plus BSC (including those who received everolimus+BSC from start to end of the study and those who received everolimus+BSC after crossover)

Reporting group title	Placebo+BSC (blinded period)

Reporting group description:

Participants received matching placebo once daily plus BSC during the blinded period

Serious adverse events	Everolimus+BSC (throughout study)	Everolimus+BSC (crossover)	Everolimus+BSC (all)
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 202 (46.04%)	1 / 6 (16.67%)	94 / 208 (45.19%)
number of deaths (all causes)	10	0	10
number of deaths resulting from adverse events	2	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 202 (2.97%)	0 / 6 (0.00%)	6 / 208 (2.88%)
occurrences causally related to treatment / all	3 / 6	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chest discomfort			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	7 / 202 (3.47%)	0 / 6 (0.00%)	7 / 208 (3.37%)
occurrences causally related to treatment / all	5 / 7	0 / 0	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organ failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	11 / 202 (5.45%)	0 / 6 (0.00%)	11 / 208 (5.29%)
occurrences causally related to treatment / all	9 / 13	0 / 0	9 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			

subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obliterative bronchiolitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	5 / 202 (2.48%)	0 / 6 (0.00%)	5 / 208 (2.40%)
occurrences causally related to treatment / all	2 / 6	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	4 / 202 (1.98%)	0 / 6 (0.00%)	4 / 208 (1.92%)
occurrences causally related to treatment / all	4 / 4	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal stoma output decreased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disturbance in attention			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 202 (3.47%)	0 / 6 (0.00%)	7 / 208 (3.37%)
occurrences causally related to treatment / all	5 / 8	0 / 0	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 202 (6.44%)	1 / 6 (16.67%)	14 / 208 (6.73%)
occurrences causally related to treatment / all	3 / 16	0 / 1	3 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	10 / 202 (4.95%)	0 / 6 (0.00%)	10 / 208 (4.81%)
occurrences causally related to treatment / all	8 / 12	0 / 0	8 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal oedema			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jejunal perforation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			

subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic necrosis			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	6 / 202 (2.97%)	1 / 6 (16.67%)	7 / 208 (3.37%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	5 / 202 (2.48%)	0 / 6 (0.00%)	5 / 208 (2.40%)
occurrences causally related to treatment / all	2 / 5	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	1 / 5	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperhidrosis			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 202 (1.98%)	0 / 6 (0.00%)	4 / 208 (1.92%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site cellulitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 202 (3.47%)	0 / 6 (0.00%)	7 / 208 (3.37%)
occurrences causally related to treatment / all	6 / 8	0 / 0	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Skin infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 202 (1.98%)	0 / 6 (0.00%)	4 / 208 (1.92%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral myocarditis			

subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 202 (0.99%)	0 / 6 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	3 / 202 (1.49%)	1 / 6 (16.67%)	4 / 208 (1.92%)
occurrences causally related to treatment / all	3 / 4	0 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 6 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo+BSC (blinded period)		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 98 (21.43%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Prostate cancer			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fatigue			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Organ failure			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Performance status decreased			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Contrast media allergy				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Ovarian cyst				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Interstitial lung disease				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obliterative bronchiolitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary alveolar haemorrhage				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary mass				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				

subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Panic attack				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stress				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Ejection fraction decreased				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stoma output decreased				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Troponin increased				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				

subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incisional hernia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure acute			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure chronic			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular disorder			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amnesia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disturbance in attention				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				

subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Ascites				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal oedema				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				

subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jejunal perforation				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic necrosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic pain				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug eruption				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperhidrosis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic skin eruption				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal pain				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchopulmonary aspergillosis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incision site cellulitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia bacterial				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral myocarditis				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				

subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypovolaemia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				

subjects affected / exposed	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Everolimus+BSC (throughout study)	Everolimus+BSC (crossover)	Everolimus+BSC (all)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 202 (97.52%)	6 / 6 (100.00%)	203 / 208 (97.60%)
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 202 (13.86%)	1 / 6 (16.67%)	29 / 208 (13.94%)
occurrences (all)	36	1	37
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 202 (22.77%)	0 / 6 (0.00%)	46 / 208 (22.12%)
occurrences (all)	67	0	67
Chills			
subjects affected / exposed	6 / 202 (2.97%)	1 / 6 (16.67%)	7 / 208 (3.37%)
occurrences (all)	6	1	7
Fatigue			
subjects affected / exposed	76 / 202 (37.62%)	2 / 6 (33.33%)	78 / 208 (37.50%)
occurrences (all)	93	2	95
Oedema peripheral			
subjects affected / exposed	81 / 202 (40.10%)	1 / 6 (16.67%)	82 / 208 (39.42%)
occurrences (all)	119	1	120
Peripheral swelling			
subjects affected / exposed	11 / 202 (5.45%)	0 / 6 (0.00%)	11 / 208 (5.29%)
occurrences (all)	13	0	13
Pyrexia			
subjects affected / exposed	49 / 202 (24.26%)	2 / 6 (33.33%)	51 / 208 (24.52%)
occurrences (all)	75	2	77
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	63 / 202 (31.19%)	1 / 6 (16.67%)	64 / 208 (30.77%)
occurrences (all)	84	1	85
Dysphonia			
subjects affected / exposed	6 / 202 (2.97%)	1 / 6 (16.67%)	7 / 208 (3.37%)
occurrences (all)	6	1	7
Dyspnoea			
subjects affected / exposed	42 / 202 (20.79%)	0 / 6 (0.00%)	42 / 208 (20.19%)
occurrences (all)	49	0	49
Epistaxis			
subjects affected / exposed	28 / 202 (13.86%)	2 / 6 (33.33%)	30 / 208 (14.42%)
occurrences (all)	42	2	44
Laryngeal pain			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	13 / 202 (6.44%)	1 / 6 (16.67%)	14 / 208 (6.73%)
occurrences (all)	15	1	16
Pleural effusion			
subjects affected / exposed	12 / 202 (5.94%)	0 / 6 (0.00%)	12 / 208 (5.77%)
occurrences (all)	12	0	12
Pneumonitis			
subjects affected / exposed	30 / 202 (14.85%)	0 / 6 (0.00%)	30 / 208 (14.42%)
occurrences (all)	40	0	40
Rhinitis allergic			
subjects affected / exposed	2 / 202 (0.99%)	1 / 6 (16.67%)	3 / 208 (1.44%)
occurrences (all)	4	1	5
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 202 (4.46%)	1 / 6 (16.67%)	10 / 208 (4.81%)
occurrences (all)	10	1	11
Insomnia			

subjects affected / exposed	20 / 202 (9.90%)	0 / 6 (0.00%)	20 / 208 (9.62%)
occurrences (all)	26	0	26
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 202 (5.94%)	0 / 6 (0.00%)	12 / 208 (5.77%)
occurrences (all)	28	0	28
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 202 (1.49%)	0 / 6 (0.00%)	3 / 208 (1.44%)
occurrences (all)	3	0	3
Blood creatinine increased			
subjects affected / exposed	11 / 202 (5.45%)	1 / 6 (16.67%)	12 / 208 (5.77%)
occurrences (all)	12	1	13
Blood urea			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Blood uric acid			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 202 (4.46%)	1 / 6 (16.67%)	10 / 208 (4.81%)
occurrences (all)	9	1	10
Weight decreased			
subjects affected / exposed	51 / 202 (25.25%)	2 / 6 (33.33%)	53 / 208 (25.48%)
occurrences (all)	53	2	55
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 202 (1.49%)	1 / 6 (16.67%)	4 / 208 (1.92%)
occurrences (all)	3	1	4
Limb injury			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Dizziness			

subjects affected / exposed	11 / 202 (5.45%)	0 / 6 (0.00%)	11 / 208 (5.29%)
occurrences (all)	15	0	15
Dysgeusia			
subjects affected / exposed	26 / 202 (12.87%)	1 / 6 (16.67%)	27 / 208 (12.98%)
occurrences (all)	28	1	29
Headache			
subjects affected / exposed	27 / 202 (13.37%)	1 / 6 (16.67%)	28 / 208 (13.46%)
occurrences (all)	34	1	35
Paraesthesia			
subjects affected / exposed	5 / 202 (2.48%)	2 / 6 (33.33%)	7 / 208 (3.37%)
occurrences (all)	5	2	7
Polyneuropathy			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Syncope			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Taste disorder			
subjects affected / exposed	13 / 202 (6.44%)	1 / 6 (16.67%)	14 / 208 (6.73%)
occurrences (all)	14	1	15
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	47 / 202 (23.27%)	0 / 6 (0.00%)	47 / 208 (22.60%)
occurrences (all)	56	0	56
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Vertigo			
subjects affected / exposed	3 / 202 (1.49%)	2 / 6 (33.33%)	5 / 208 (2.40%)
occurrences (all)	3	2	5
Eye disorders			
Blindness			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Dry eye			

subjects affected / exposed	4 / 202 (1.98%)	1 / 6 (16.67%)	5 / 208 (2.40%)
occurrences (all)	4	1	5
Eye pain			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Visual impairment			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 202 (0.00%)	0 / 6 (0.00%)	0 / 208 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	38 / 202 (18.81%)	1 / 6 (16.67%)	39 / 208 (18.75%)
occurrences (all)	56	1	57
Abdominal pain upper			
subjects affected / exposed	21 / 202 (10.40%)	0 / 6 (0.00%)	21 / 208 (10.10%)
occurrences (all)	30	0	30
Aphthous ulcer			
subjects affected / exposed	8 / 202 (3.96%)	3 / 6 (50.00%)	11 / 208 (5.29%)
occurrences (all)	12	5	17
Constipation			
subjects affected / exposed	25 / 202 (12.38%)	2 / 6 (33.33%)	27 / 208 (12.98%)
occurrences (all)	31	2	33
Diarrhoea			
subjects affected / exposed	88 / 202 (43.56%)	3 / 6 (50.00%)	91 / 208 (43.75%)
occurrences (all)	130	6	136
Dry mouth			
subjects affected / exposed	18 / 202 (8.91%)	0 / 6 (0.00%)	18 / 208 (8.65%)
occurrences (all)	19	0	19
Dyspepsia			
subjects affected / exposed	11 / 202 (5.45%)	1 / 6 (16.67%)	12 / 208 (5.77%)
occurrences (all)	15	1	16
Flatulence			
subjects affected / exposed	7 / 202 (3.47%)	1 / 6 (16.67%)	8 / 208 (3.85%)
occurrences (all)	7	1	8

Mouth ulceration			
subjects affected / exposed	18 / 202 (8.91%)	0 / 6 (0.00%)	18 / 208 (8.65%)
occurrences (all)	29	0	29
Nausea			
subjects affected / exposed	58 / 202 (28.71%)	0 / 6 (0.00%)	58 / 208 (27.88%)
occurrences (all)	80	0	80
Proctalgia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	113 / 202 (55.94%)	2 / 6 (33.33%)	115 / 208 (55.29%)
occurrences (all)	189	5	194
Tongue ulceration			
subjects affected / exposed	2 / 202 (0.99%)	1 / 6 (16.67%)	3 / 208 (1.44%)
occurrences (all)	2	1	3
Toothache			
subjects affected / exposed	11 / 202 (5.45%)	2 / 6 (33.33%)	13 / 208 (6.25%)
occurrences (all)	11	2	13
Vomiting			
subjects affected / exposed	33 / 202 (16.34%)	0 / 6 (0.00%)	33 / 208 (15.87%)
occurrences (all)	41	0	41
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	20 / 202 (9.90%)	0 / 6 (0.00%)	20 / 208 (9.62%)
occurrences (all)	23	0	23
Dry skin			
subjects affected / exposed	18 / 202 (8.91%)	0 / 6 (0.00%)	18 / 208 (8.65%)
occurrences (all)	23	0	23
Eczema			
subjects affected / exposed	6 / 202 (2.97%)	1 / 6 (16.67%)	7 / 208 (3.37%)
occurrences (all)	6	1	7
Erythema			
subjects affected / exposed	11 / 202 (5.45%)	0 / 6 (0.00%)	11 / 208 (5.29%)
occurrences (all)	12	0	12
Nail ridging			

subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	2	3
Pruritus			
subjects affected / exposed	37 / 202 (18.32%)	2 / 6 (33.33%)	39 / 208 (18.75%)
occurrences (all)	45	2	47
Rash			
subjects affected / exposed	62 / 202 (30.69%)	3 / 6 (50.00%)	65 / 208 (31.25%)
occurrences (all)	90	5	95
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	8 / 202 (3.96%)	0 / 6 (0.00%)	8 / 208 (3.85%)
occurrences (all)	10	0	10
Haematuria			
subjects affected / exposed	11 / 202 (5.45%)	1 / 6 (16.67%)	12 / 208 (5.77%)
occurrences (all)	12	1	13
Proteinuria			
subjects affected / exposed	18 / 202 (8.91%)	0 / 6 (0.00%)	18 / 208 (8.65%)
occurrences (all)	29	0	29
Endocrine disorders			
Carcinoid syndrome			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 202 (15.35%)	0 / 6 (0.00%)	31 / 208 (14.90%)
occurrences (all)	45	0	45
Back pain			
subjects affected / exposed	34 / 202 (16.83%)	0 / 6 (0.00%)	34 / 208 (16.35%)
occurrences (all)	39	0	39
Bursitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Musculoskeletal pain			
subjects affected / exposed	5 / 202 (2.48%)	1 / 6 (16.67%)	6 / 208 (2.88%)
occurrences (all)	6	2	8
Myalgia			

subjects affected / exposed	15 / 202 (7.43%)	0 / 6 (0.00%)	15 / 208 (7.21%)
occurrences (all)	17	0	17
Osteoarthritis			
subjects affected / exposed	2 / 202 (0.99%)	2 / 6 (33.33%)	4 / 208 (1.92%)
occurrences (all)	2	2	4
Osteoporosis			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Pain in extremity			
subjects affected / exposed	19 / 202 (9.41%)	0 / 6 (0.00%)	19 / 208 (9.13%)
occurrences (all)	24	0	24
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 202 (3.96%)	2 / 6 (33.33%)	10 / 208 (4.81%)
occurrences (all)	10	3	13
Cystitis			
subjects affected / exposed	7 / 202 (3.47%)	1 / 6 (16.67%)	8 / 208 (3.85%)
occurrences (all)	14	3	17
Gastrointestinal viral infection			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Influenza			
subjects affected / exposed	9 / 202 (4.46%)	2 / 6 (33.33%)	11 / 208 (5.29%)
occurrences (all)	12	2	14
Nasopharyngitis			
subjects affected / exposed	22 / 202 (10.89%)	2 / 6 (33.33%)	24 / 208 (11.54%)
occurrences (all)	36	12	48
Pneumonia			
subjects affected / exposed	18 / 202 (8.91%)	0 / 6 (0.00%)	18 / 208 (8.65%)
occurrences (all)	20	0	20
Pulpitis dental			
subjects affected / exposed	0 / 202 (0.00%)	1 / 6 (16.67%)	1 / 208 (0.48%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	4 / 202 (1.98%)	1 / 6 (16.67%)	5 / 208 (2.40%)
occurrences (all)	4	1	5

Upper respiratory tract infection			
subjects affected / exposed	18 / 202 (8.91%)	1 / 6 (16.67%)	19 / 208 (9.13%)
occurrences (all)	25	1	26
Urinary tract infection			
subjects affected / exposed	23 / 202 (11.39%)	1 / 6 (16.67%)	24 / 208 (11.54%)
occurrences (all)	36	3	39
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	53 / 202 (26.24%)	1 / 6 (16.67%)	54 / 208 (25.96%)
occurrences (all)	60	1	61
Hypercholesterolaemia			
subjects affected / exposed	16 / 202 (7.92%)	1 / 6 (16.67%)	17 / 208 (8.17%)
occurrences (all)	16	1	17
Hypercreatininaemia			
subjects affected / exposed	1 / 202 (0.50%)	1 / 6 (16.67%)	2 / 208 (0.96%)
occurrences (all)	1	1	2
Hyperglycaemia			
subjects affected / exposed	24 / 202 (11.88%)	1 / 6 (16.67%)	25 / 208 (12.02%)
occurrences (all)	39	1	40
Hypertriglyceridaemia			
subjects affected / exposed	12 / 202 (5.94%)	1 / 6 (16.67%)	13 / 208 (6.25%)
occurrences (all)	17	1	18
Hypokalaemia			
subjects affected / exposed	21 / 202 (10.40%)	3 / 6 (50.00%)	24 / 208 (11.54%)
occurrences (all)	24	3	27
Hypomagnesaemia			
subjects affected / exposed	5 / 202 (2.48%)	1 / 6 (16.67%)	6 / 208 (2.88%)
occurrences (all)	8	1	9

Non-serious adverse events	Placebo+BSC (blinded period)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 98 (82.65%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 98 (10.20%)		
occurrences (all)	14		
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	36 / 98 (36.73%)		
occurrences (all)	46		
Oedema peripheral			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	7		
Peripheral swelling			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	10		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 98 (20.41%)		
occurrences (all)	25		
Dysphonia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	11 / 98 (11.22%)		
occurrences (all)	13		
Epistaxis			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		

Laryngeal pain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Pneumonitis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	3		
Rhinitis allergic			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	8		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	7		
Blood creatinine increased			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Blood urea			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Blood uric acid			

subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	11 / 98 (11.22%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	6		
Dysgeusia			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	15 / 98 (15.31%)		
occurrences (all)	21		
Paraesthesia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Syncope			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	2		
Taste disorder			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	10		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Eye disorders			
Blindness			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	17 / 98 (17.35%)		
occurrences (all)	19		
Abdominal pain upper			

subjects affected / exposed	11 / 98 (11.22%)			
occurrences (all)	14			
Aphthous ulcer				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Constipation				
subjects affected / exposed	19 / 98 (19.39%)			
occurrences (all)	21			
Diarrhoea				
subjects affected / exposed	30 / 98 (30.61%)			
occurrences (all)	54			
Dry mouth				
subjects affected / exposed	5 / 98 (5.10%)			
occurrences (all)	5			
Dyspepsia				
subjects affected / exposed	5 / 98 (5.10%)			
occurrences (all)	7			
Flatulence				
subjects affected / exposed	6 / 98 (6.12%)			
occurrences (all)	6			
Mouth ulceration				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	16 / 98 (16.33%)			
occurrences (all)	24			
Proctalgia				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	3			
Stomatitis				
subjects affected / exposed	19 / 98 (19.39%)			
occurrences (all)	22			
Tongue ulceration				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Toothache				

subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	10 / 98 (10.20%)		
occurrences (all)	16		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	5		
Eczema			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Nail ridging			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	9		
Rash			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	10		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	5		
Haematuria			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences (all)	7		
Proteinuria			

subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Endocrine disorders			
Carcinoid syndrome			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	9		
Back pain			
subjects affected / exposed	14 / 98 (14.29%)		
occurrences (all)	15		
Bursitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences (all)	6		
Osteoarthritis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	6		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Cystitis			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Gastrointestinal viral infection			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences (all)	6		
Pneumonia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Pulpitis dental			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	9		
Urinary tract infection			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 98 (17.35%)		
occurrences (all)	22		
Hypercholesterolaemia			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Hypercreatininaemia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		

Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 7		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2012	This amendment included changes aimed to improve consistency across the study, apply the Novartis guidance on prevention of pregnancy in clinical trials, modify the timing of the planned interim analysis, and to better align the study with standard of care. The amendment also included the addition of PK (sampling and analysis).
28 January 2014	Due to the rapid enrollment, the DMC meeting for the interim efficacy analysis (at 80% of the events) was predicted to occur when the number of events (N=176) for the final PFS analysis was already observed. Therefore, the interim analysis for PFS was canceled. The DMC and the Steering Committees agreed with the recommendation to cancel the interim analysis for PFS. Due to the cancelation of the PFS interim analysis, the first of the planned interim analyses for OS was canceled and replaced by a later interim analysis at 50% of the final OS events (at approximately 95 OS events)
06 May 2016	Following the crossover of patients on treatment with placebo to open-label treatment with everolimus (per DMC recommendation, 03-Jun-2015), the Visit Evaluation Schedule was updated to report a new End of Treatment visit, specific for patients who will discontinue the open-label treatment. All patients (still on treatment or in survival follow up) will be followed, as per protocol, until the end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/ for complete trial results.

Notes: