Clinical trial results:
A randomized double-blind phase III study of everolimus (RAD001) 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)

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/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2006-006819-75
Trial protocol	NL IT DE ES FR GR BE GB SK SE
Global end of trial date	05 March 2014

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001C2324

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00510068
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine whether treatment with everolimus (RAD001) 10 mg/d plus best supportive care (BSC) prolongs progression free survival (PFS) compared to treatment with placebo plus BSC in patients with advanced pancreatic neuroendocrine tumor (NET).

There were two study periods: randomized core, followed by open label.

Core: Four hundred ten (410) patients were randomized and constituted the full analysis set (FAS), with 207 patients randomized to everolimus and 203 randomized to placebo.

Open label: Subsequently, 172 patients from placebo and 53 who were initially randomized to 10 mg everolimus arm were allowed to continue on 10 mg open label everolimus.

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. The elements of the study design were consistent with the framework of a life-threatening disease with an unmet medical need whereby a double-blind, placebo-controlled study design is considered to be the gold standard required by health authorities to demonstrate the efficacy of a new therapeutic agent. Dose adjustments and interruptions for patients that could not tolerate treatment were part of the study design, as well as guidance for managing adverse events with supportive care and following adverse events to resolution. An independent data monitoring committee performed ongoing safety review.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	30 July 2007
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	Brazil: 1
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Thailand: 2

Country: Number of subjects enrolled	United States: 165
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	410
EEA total number of subjects	154

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)	299
From 65 to 84 years	108
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Four hundred ten (410) patients were randomized and constituted the full analysis set (FAS), with 207 patients randomized to everolimus and 203 randomized to placebo. Subsequently, 172 patients from placebo and 53 who were initially randomized to 10 mg everolimus arm were allowed to continue on 10 mg open label everolimus.

Pre-assignment

Screening details:

To be eligible for the study, adult patients must have advanced (unresectable or metastatic) biopsy-proven pancreatic neuroendocrine tumor (NET), with measurable disease by radiologic assessment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus 10 mg/Day

Arm description:

Participants received 10 mg per day of everolimus plus best supportive care. Patients received their first dose of everolimus at Visit 2 (Cycle 1 Day 1).

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

Dosage and administration details:

A 10-mg dose of everolimus was given by continuous oral daily dosing of two 5-mg tablets.

Arm title	Placebo Comparator

Arm description:

Participants received matching placebo to everolimus daily plus best supportive care.

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:

A 10-mg dose of matching placebo to everolimus was given by continuous oral daily dosing of two 5-mg tablets.

Number of subjects in period 1	Everolimus 10 mg/Day	Placebo Comparator
Started	207	203
Completed	0	0
Not completed	207	203
Final primary analysis	52	18
Consent withdrawn by subject	8	6
Disease progression	98	169
Adverse Event	37	7
Death	4	3
Protocol Violation	6	-
Lost to follow-up	1	-
Abnormal test procedure result(s)	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus 10 mg/Day
Reporting group description:	
Participants received 10 mg per day of everolimus plus best supportive care. Patients received their first dose of everolimus at Visit 2 (Cycle 1 Day 1).	
Reporting group title	Placebo Comparator
Reporting group description:	
Participants received matching placebo to everolimus daily plus best supportive care.	

Reporting group values	Everolimus 10 mg/Day	Placebo Comparator	Total
Number of subjects	207	203	410
Age categorical			
Four hundred ten (410) patients were randomized and constituted the full analysis set (FAS), with 207 patients randomized to everolimus and 203 randomized to placebo and are represented in the baseline characteristics.			
Units: Subjects			
<65 years	146	153	299
>=65 years	61	50	111
Age continuous			
Four hundred ten (410) patients were randomized and constituted the full analysis set (FAS), with 207 patients randomized to everolimus and 203 randomized to placebo and are represented in the baseline characteristics. the EMA result system autopopulates the "-" and will not allow the entry of the mean age for the trial, which is 56.6 (standard deviation: 11.8).			
Units: years			
arithmetic mean	57.1	56.2	
standard deviation	± 12.2	± 11.4	-
Gender categorical			
Four hundred ten (410) patients were randomized and constituted the full analysis set (FAS), with 207 patients randomized to everolimus and 203 randomized to placebo and are represented in the baseline characteristics.			
Units: Subjects			
Female	97	86	183
Male	110	117	227
Race/Ethnicity			
Four hundred ten (410) patients were randomized and constituted the full analysis set (FAS), with 207 patients randomized to everolimus and 203 randomized to placebo and are represented in the baseline characteristics.			
Units: Subjects			
Caucasian	156	166	322
Asian	40	34	74
Black	9	2	11
Other	2	1	3

End points

End points reporting groups

Reporting group title	Everolimus 10 mg/Day

Reporting group description:

Participants received 10 mg per day of everolimus plus best supportive care. Patients received their first dose of everolimus at Visit 2 (Cycle 1 Day 1).

Reporting group title	Placebo Comparator

Reporting group description:

Participants received matching placebo to everolimus daily plus best supportive care.

Subject analysis set title	Open-label Everolimus 10 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligible patients from the core study continued to an open label period: 172 from the placebo arm and 53 who were initially randomized to everolimus arm. Participants received 10 mg per day of everolimus plus best supportive care. Patients received their first dose of everolimus at Visit 2 (Cycle 1 Day 1). These patients were included in the open-label analysis set. Patients discontinued the study from this arm due to death (7), new cancer therapy (7), administrative problems (17), protocol violation (2), abnormal laboratory values (1), withdrawal of consent (21), disease progression (124), or adverse event (46).

Subject analysis set title	Everolimus 5 mg/Day
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patient C2324-0425-00007: received the 5-mg daily dose (rather than 10 mg) for the full PK profile.

Primary: Time to Progression-Free Survival (PFS) per Investigator Using Kaplan-Meier

End point title	Time to Progression-Free Survival (PFS) per Investigator Using Kaplan-Meier

End point description:

Time to Progression Free Survival (PFS) based as per investigator using Kaplan-Meier methodology. Progression of disease is defined as the time from study start to the date of first documented progression of disease or death due to any cause. Progression of disease is defined by RECIST criteria: Progression = 20% increase in the sum of the longest diameter of all target lesions, from the smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or progression of non-target lesions. These data represent the full analysis set.

End point type	Primary

End point timeframe:

Time from randomisation to dates of disease progression, death from any cause or last tumor assessment, reported between day of first patient randomised, 17 August 2007, until cut-off date 28 February 2010.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[1]	203[2]		
Units: months				
median (confidence interval 95%)				
PFS per investigator using K-M	11.04 (8.41 to 13.86)	4.6 (3.06 to 5.39)		

Notes:

[1] - Full analysis set. PFS based as per investigator using Kaplan-Meier methodology.
[2] - Full analysis set. PFS based as per investigator using Kaplan-Meier methodology.

Statistical analyses

Statistical analysis title	Local Investigator Assessment of PFS
Comparison groups	Everolimus 10 mg/Day v Placebo Comparator
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Stratified Unadjusted Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.45

Secondary: Percentage of Participants with Objective Response Rate (Complete or Partial Response)

End point title	Percentage of Participants with Objective Response Rate (Complete or Partial Response)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Objective Response defined by RECIST criteria: Partial response (PR) must have ≥ 30% decrease in the sum of the longest diameter of all target lesions, from the baseline sum. Complete response (CR) must have disappearance of all target and non-target lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments within 4 weeks . Progression = 20% increase in the sum of the longest diameter of all target lesions, from the smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or progression of non-target lesions.

End point type	Secondary

End point timeframe:

Time from randomisation to dates of disease progression, death from any cause or last tumor assessment, reported between day of first patient randomised, 17 August 2007, until cut-off date 28 February 2010.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[3]	203[4]		
Units: percentage of participants				
number (confidence interval 95%)				
Overall response rate	4.8 (2.3 to 8.7)	2 (0.5 to 5)		

Notes:

[3] - Full analysis set. Includes all patients with complete (CR) or partial response (PR).

[4] - Full analysis set. Includes all patients with complete (CR) or partial response (PR).

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Overall Survival

End point title	Time to Overall Survival

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Overall survival (OS) was defined as the time from date of randomization to the date of death due to any cause. Analyses were performed using all deaths in the full analysis set (FAS) population regardless of whether they were observed during the double- blind treatment period, the open-label treatment period, the post-treatment evaluations, or the survival follow-up period.

End point type	Secondary

End point timeframe:

Baseline to death- no time limit.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[5]	203[6]		
Units: months				
median (confidence interval 95%)				
Time to Overall Survival (months)	44.02 (35.61 to 51.75)	37.68 (29.14 to 45.77)		

Notes:

[5] - Full analysis set.

[6] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival According to Ki-67 Levels Categorized as Less than or Equal to 2%, >2% to Less Than or Equal to 5% and >5%

End point title	Progression Free Survival According to Ki-67 Levels Categorized as Less than or Equal to 2%, >2% to Less Than or Equal to 5% and >5%

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. The level of Ki 67 expression for evaluable tumor samples were analyzed towards progression free survival (PFS) as per local investigator assessment. The Ki-67 protein is a cellular marker for proliferation. It is strictly associated with cell proliferation. During interphase, the Ki-67 antigen can be exclusively detected within the cell nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. Baseline Ki 67 levels were categorized as: less than or equal to 2%, > 2% to less than or equal to 5% and > 5%. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Time from randomisation to dates of disease progression, death from any cause or last tumor assessment, reported between day of first patient randomised, 17 August 2007, until cut-off date 28 February 2010.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[7]	203[8]		
Units: months				
median (confidence interval 95%)				
Ki67 <=2% (n: 7, 17)	12.52 (3.42 to 14.75)	3.68 (2.86 to 5.52)		
2% <Ki67 <=5% (n: 24, 13)	10.94 (5.55 to 16.59)	8.48 (3.78 to 13.83)		
Ki67 >5% (n: 20, 22)	7.69 (5.59 to 999999)	3.15 (2.79 to 5.55)		

Notes:

[7] - Full analysis set. Immunohistochemical and genetic analyses indicating activation of mTOR pathway.
[8] - Full analysis set. Immunohistochemical and genetic analyses indicating activation of mTOR pathway.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival According to Chromagranin A (CgA) Baseline Level and According to CgA Early Response

End point title	Progression Free Survival According to Chromagranin A (CgA) Baseline Level and According to CgA Early Response

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. Baseline levels of serum CgA SE were characterized towards progression free survival (PFS) as per local investigator assessment, relative to the upper limited of normal (ULN). CgA levels exceeding 2 x ULN were considered to be 'Elevated' otherwise considered as "Non-elevated". An ‘early response’ (applicable to only those patients with elevated levels at baseline) was defined as a decrease of greater than or equal to 30% from baseline to Cycle 2 Day 1 or normalization by Cycle 2 Day 1. CgA is widely expressed in well-differentiated pancreatic NET. CgA is present in the secretory granules of neuroendocrine cells. Pancreatic NET patients often present with elevated circulating levels of CgA in their blood. Baseline levels of these biomarkers are considered as prognostic factors. EMA directed use of 999999 as the EU results system will not accept “not estimable”.

End point type	Secondary

End point timeframe:

Time from randomisation to dates of disease progression, death from any cause or last tumor assessment, reported between day of first patient randomised, 17 August 2007, until cut-off date 28 February 2010.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[9]	203[10]		
Units: months				
median (confidence interval 95%)				
CgA Levels at baseline:CgA <= 2x ULN (n:121, 97)	11.17 (8.54 to 16.49)	4.9 (2.99 to 5.55)		
CgA levels at baseline: CgA> 2x ULN (n:84, 103)	8.54 (7.69 to 13.8)	4.34 (2.86 to 5.39)		
Early CgA response:Response (n: 48, 22)	8.54 (7.56 to 14)	5.7 (3.19 to 8.54)		
Early CgA response: Non-Response (n:40, 82)	11.14 (6.9 to 999999)	3.19 (2.83 to 5.36)		

Notes:

[9] - Full analysis set

[10] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival According to Neuron Specific Enolase (NSE) Tumor Marker Baseline Level According to NSE Early Response

End point title	Progression Free Survival According to Neuron Specific Enolase (NSE) Tumor Marker Baseline Level According to NSE Early Response

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. Baseline levels of serum NSE were characterized towards PFS as per local investigator assessment, relative to the upper limited of normal (ULN). NSE levels exceeding ULN were considered to be 'Elevated' otherwise considered as "Non-elevated". An ‘early response’ (applicable to only those patients with elevated levels at baseline) was defined as a decrease of greater than or equal to 30% from baseline to Cycle 2 Day 1 or normalization by Cycle 2 Day 1. NSE is widely expressed in well-differentiated pancreatic NET. NSE is usually expressed in the cytoplasm. Pancreatic NET patients often present with elevated circulating levels of NSE in their blood. Baseline levels of these biomarkers are considered as prognostic factors.

End point type	Secondary

End point timeframe:

Time from randomisation to dates of disease progression, death from any cause or last tumor assessment, reported between day of first patient randomised, 17 August 2007, until cut-off date 28 February 2010.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[11]	203[12]		
Units: months				
median (confidence interval 95%)				
NSE Levels at baseline: <= ULN (n: 155, 138)	13.86 (10.81 to 18.1)	5.36 (3.78 to 5.55)		
NSE levels at baseline: >ULN (n: 48, 56)	8.11 (4.24 to 11.17)	2.83 (2.6 to 3.06)		
Early NSE response:Response (n: 24, 16)	8.11 (4.24 to 11.4)	3.06 (2.23 to 5.36)		

Early NSE response: Non-Response (n:16, 27)	3.79 (2.6 to 13.8)	2.58 (1.84 to 2.83)		

Notes:

[11] - The Full Analysis Set (FAS) consisted of all patients who were randomized.

[12] - The Full Analysis Set (FAS) consisted of all patients who were randomized.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs), serious adverse events (SAEs)

End point title	Number of participants with adverse events (AEs), serious adverse events (SAEs)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the open label safety set. Adverse events are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards.

End point type	Secondary

End point timeframe:

On or after the start of double-blind study medication until no later than 28 days after double-blind study medication discontinuation.

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[13]	203[14]		
Units: Participants				
Adverse events (AEs)	203	198		
Death	111	23		
Serious Adverse Events	84	52		

Notes:

[13] - Safety Set: all patients receiving any study drug and at least 1 post-baseline safety assessment

[14] - Safety Set: all patients receiving any study drug and at least 1 post-baseline safety assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs), serious adverse events (SAEs) (Open-label Period)

End point title	Number of participants with adverse events (AEs), serious adverse events (SAEs) (Open-label Period)

End point description:

Adverse events are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward

medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. The open-label set was used to summarize the safety analyses performed on data collected in the open-label period of the study: the open-label set included only patients who received at least one dose of open-label everolimus 10 mg and had at least one safety assessment during the open-label period of the study.

End point type	Secondary

End point timeframe:

On or after the start of open-label study medication until no later than 28 days after open-label study medication discontinuation.

End point values	Open-label Everolimus 10 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	225			
Units: Participants				
Adverse events (AEs)	221			
Death	122			
Serious Adverse Events	108			

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Pharmacokinetics (PK) Parameter: AUC0-t last

End point title	Evaluation of Pharmacokinetics (PK) Parameter: AUC0-t last[15]

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the safety analysis set. The PK parameters for a full PK profile at steady-state were determined in blood using non compartmental methods.
This PK parameter is area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-t last). Analysis population included The Safety Set consisted of all patients who received any study drug and had at least one postbaseline safety assessment. Patient C2324-0425-00007: received the 5-mg daily dose (rather than 10 mg) for the full PK profile. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Day 1 of every cycle (28 days/cycle) throughout the study.

Notes:

[15] - 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: PK analyses cannot be done with the placebo group, since there shouldn't be any everolimus in the patient's system.

End point values	Everolimus 10 mg/Day	Everolimus 5 mg/Day		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7[16]	1[17]		
Units: ng .h /mL				
arithmetic mean (standard deviation)				
Evaluation of PK Parameter: AUC0-t last	594 (± 313)	481 (± 999999)		

Notes:

[16] - Safety analysis set

[17] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Pharmacokinetics (PK) Parameters: Cmax, Cmin

End point title	Evaluation of Pharmacokinetics (PK) Parameters: Cmax,

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the safety analysis set. The PK parameters for a full PK profile at steady-state were determined in blood using non compartmental methods. The PK parameter: maximum (peak) drug concentration (Cmax) and minimum (trough) drug concentration (Cmin). This analysis included the Safety Set, which consisted of all patients who received any study drug and had at least one postbaseline safety assessment. Patient C2324-0425-00007: received the 5-mg daily dose (rather than 10 mg) for the full PK profile. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Day 1 of every cycle (28 days/cycle) throughout the study

Notes:

[18] - 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: PK analyses cannot be done with the placebo group, since there shouldn't be any everolimus in the patient's system.

End point values	Everolimus 10 mg/Day	Everolimus 5 mg/Day		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7[19]	1[20]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax	62.4 (± 18.5)	27.4 (± 999999)		
Cmin	9.8 (± 4.95)	12.2 (± 999999)		

Notes:

[19] - Safety analysis set

[20] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Pharmacokinetics (PK) Parameter: CL/F

End point title	Evaluation of Pharmacokinetics (PK) Parameter: CL/F[21]

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the safety analysis set. The PK parameters for a full PK profile at steady-state were determined in blood using non compartmental methods. The PK parameter clearance of distribution expressed as a function of bioavailability (CL/F). The analysis population included the Safety Set, which consisted of all patients who received any study drug and had at least one postbaseline safety assessment. Patient C2324-0425-00007: received the 5-mg daily dose (rather than 10 mg) for the full PK profile. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Day 1 of every cycle (28 days/cycle) throughout the study.

Notes:

[21] - 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: PK analyses cannot be done with the placebo group, since there shouldn't be any everolimus in the patient's system.

End point values	Everolimus 10 mg/Day	Everolimus 5 mg/Day		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7[22]	1[23]		
Units: L/h				
arithmetic mean (standard deviation)				
Evaluation of PK Parameter: CL/F	20.2 (± 7.7)	10.7 (± 999999)		

Notes:

[22] - Safety analysis set

[23] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Pharmacokinetics (PK) Parameter: tmax -time to maximum (peak) drug

End point title	Evaluation of Pharmacokinetics (PK) Parameter: tmax -time to maximum (peak) drug[24]

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the safety analysis set. The PK parameters for a full PK profile at steady-state were determined in blood using non compartmental methods. Values for tmax where summarized in median (range). The analysis population included the Safety Set, which consisted of all patients who received any study drug and had at least one postbaseline safety assessment. Patient C2324-0425-00007: received the 5-mg daily dose (rather than 10 mg) for the full PK profile. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Day 1 of every cycle (28 days/cycle) throughout the study.

Notes:

[24] - 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: PK analyses cannot be done with the placebo group, since there shouldn't be any everolimus in the patient's system.

End point values	Everolimus 10 mg/Day	Everolimus 5 mg/Day		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7[25]	1[26]		
Units: hours				
median (full range (min-max))				
tmax-time to maximum (peak) drug concentraion	1.17 (0.5 to 24)	3 (0.999999 to 999999)		

Notes:

[25] - Safety analysis set

[26] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of time to definitive deterioration of WHO performance status using Kaplan-Meier

End point title	Analysis of time to definitive deterioration of WHO performance status using Kaplan-Meier

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Time to definitive worsening is defined as a definitive increase in performance status from a baseline of 0 or 1 to WHO >= 2, or from a baseline value of 2 to WHO >= 3. If no earlier deterioration, patients were censored at end of follow-up or at start of further antineoplastic therapy. Rates of patients with no deterioration at 3 and 6 months were computed using Kaplan-Meier method. Grade 0: Able to carry out all activity without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory & able to do light work; Grade 2: Ambulatory & capable of all self-care but unable to carry out any work. Up & about more than 50% of waking hours; Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; Grade 4: Completely disabled and cannot carry on any self-care; totally confined to bed or chair. Analysis population was the full analysis set.

End point type	Secondary

End point timeframe:

3 months, 6 months

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[27]	203[28]		
Units: % of participants with no deterioration				
arithmetic mean (confidence interval 95%)				
Month 3	94.4 (90 to 96.8)	91.8 (86.8 to 95)		
Month 6	90.6 (85.2 to 94)	86.3 (79.3 to 91)		

Notes:

[27] - Full analysis set

[28] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma angiogenesis marker: basic fibroblast growth factor (bFGF)

End point title	Plasma angiogenesis marker: basic fibroblast growth factor (bFGF)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. This biomarker is related to angiogenesis pathway, was analyzed to determine the effects of everolimus on plasma antiangiogenic molecules. The analysis population included the full analysis set which consists of all patients who were randomized.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[29]	203[30]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n:198, 195)	52.59 (± 101.659)	51.49 (± 78.049)		
Cycle 2 Day 1 (n: 185, 184)	38.43 (± 51.809)	58.33 (± 72.938)		
Cycle 3 Day 1 (n: 185, 174)	51.97 (± 89.064)	59.08 (± 72.495)		
Cycle 4 Day 1 (n: 171, 159)	51.28 (± 82.139)	54.58 (± 75.35)		

Notes:

[29] - Full analysis set

[30] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma angiogenesis marker: placental growth factor (PLGF)

End point title	Plasma angiogenesis marker: placental growth factor (PLGF)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. This biomarker is related to angiogenesis pathway, was analyzed to determine the effects of everolimus on plasma antiangiogenic molecules. The analysis population was the full analysis set and consisted of all patients who were randomized.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[31]	203[32]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n:198, 195)	45.82 (± 282.084)	32.92 (± 52.586)		
Cycle 2 Day 1 (n: 185, 184)	25.78 (± 33.42)	35.38 (± 57.135)		
Cycle 3 Day 1 (n: 185, 174)	26.55 (± 28.839)	33.84 (± 65.361)		
Cycle 4 Day 1 (n: 171, 159)	25.69 (± 18.312)	35.47 (± 67.314)		

Notes:

[31] - Full analysis set

[32] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma angiogenesis marker: soluble vascular endothelial growth factor receptor 1 (sVEGFR1)

End point title	Plasma angiogenesis marker: soluble vascular endothelial growth factor receptor 1 (sVEGFR1)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. This biomarker is related to angiogenesis pathway, was analyzed to determine the effects of everolimus on plasma antiangiogenic molecules. The analysis population includes the full analysis set, which consists of all patients who were randomized.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[33]	203[34]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n:198, 195)	264.18 (± 272.19)	256.69 (± 187.866)		
Cycle 2 Day 1 (n: 185, 184)	307.46 (± 808.316)	299.03 (± 541.933)		
Cycle 3 Day 1 (n: 185, 174)	263.81 (± 187.329)	253.37 (± 250.841)		
Cycle 4 Day 1 (n: 171, 159)	258.03 (± 223.98)	242.17 (± 163.561)		

Notes:

[33] - Full analysis set

[34] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma angiogenesis marker: soluble vascular endothelial growth factor receptor 2 (sVEGFR2)

End point title	Plasma angiogenesis marker: soluble vascular endothelial growth factor receptor 2 (sVEGFR2)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. This biomarker is related to angiogenesis pathway, was analyzed to determine the effects of everolimus on plasma antiangiogenic molecules. The analysis population included the full analysis set, which consists of all patients who were randomized.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[35]	203[36]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n:197, 193)	30061.3 (± 8607.379)	31299.61 (± 9091.46)		
Cycle 2 Day 1 (n: 185, 183)	22691.18 (± 6793.409)	30223.21 (± 8447.992)		
Cycle 3 Day 1 (n: 185, 173)	22021.23 (± 6393.414)	29264.67 (± 8408.405)		
Cycle 4 Day 1 (n: 172, 158)	21218.17 (± 6249.977)	28308.58 (± 8477.049)		

Notes:

[35] - Full Analysis Set

[36] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Angiogenesis Marker: Vascular Endothelial Growth Factor (VEGF)

End point title	Plasma Angiogenesis Marker: Vascular Endothelial Growth Factor (VEGF)

End point description:

No statistical analysis provided for this endpoint as per EMA requirements. Data presented represent the full analysis set. This biomarker is related to angiogenesis pathway, was analyzed to determine the effects of everolimus on plasma antiangiogenic molecules.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1

End point values	Everolimus 10 mg/Day	Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[37]	203[38]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n:198, 195)	265.09 (± 283.123)	326.16 (± 323.891)		
Cycle 2 Day 1 (n: 185, 184)	243.03 (± 183.01)	326.78 (± 377.752)		
Cycle 3 Day 1 (n: 185, 174)	280.18 (± 268.582)	292.27 (± 286.154)		
Cycle 4 Day 1 (n: 171, 159)	283.51 (± 326.634)	319.6 (± 325.409)		

Notes:

[37] - Full Analysis Set

[38] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Everolimus 10 mg/Day

Reporting group description:

Everolimus 10 mg

Reporting group title	Placebo Comparator

Reporting group description:

Placebo

Reporting group title	Open-Label Everolimus 10 mg/Day

Reporting group description:

Open-Label Everolimus 10 mg

Serious adverse events	Everolimus 10 mg/Day	Placebo Comparator	Open-Label Everolimus 10 mg/Day
Total subjects affected by serious adverse events			
subjects affected / exposed	84 / 204 (41.18%)	52 / 203 (25.62%)	108 / 225 (48.00%)
number of deaths (all causes)	12	4	15
number of deaths resulting from adverse events	1	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 204 (0.00%)	2 / 203 (0.99%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrinoma			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic neuroendocrine tumour metastatic			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm ruptured			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 204 (2.45%)	2 / 203 (0.99%)	6 / 225 (2.67%)
occurrences causally related to treatment / all	2 / 5	0 / 2	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Device occlusion			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 204 (0.00%)	2 / 203 (0.99%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Generalised oedema			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	8 / 204 (3.92%)	3 / 203 (1.48%)	8 / 225 (3.56%)
occurrences causally related to treatment / all	2 / 8	0 / 3	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Thrombosis in device			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cough			
subjects affected / exposed	2 / 204 (0.98%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	6 / 204 (2.94%)	2 / 203 (0.99%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	3 / 7	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	3 / 204 (1.47%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal obstruction			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 204 (0.98%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			

subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	7 / 204 (3.43%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	6 / 7	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 204 (2.45%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	3 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 204 (0.98%)	1 / 203 (0.49%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			

subjects affected / exposed	3 / 204 (1.47%)	3 / 203 (1.48%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listless			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ammonia increased			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			

subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			

subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Branchial cyst			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 204 (0.98%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocarditis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dysfunction			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			

subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 204 (0.00%)	2 / 203 (0.99%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiduritis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic coma			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 204 (3.43%)	3 / 203 (1.48%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	6 / 9	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic anaemia			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular fibrosis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmoplegia			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia obstructive			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	6 / 204 (2.94%)	5 / 203 (2.46%)	13 / 225 (5.78%)
occurrences causally related to treatment / all	1 / 6	1 / 5	3 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 204 (0.98%)	2 / 203 (0.99%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal rigidity			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			

subjects affected / exposed	3 / 204 (1.47%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 69	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 204 (2.45%)	2 / 203 (0.99%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	2 / 5	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			

subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 204 (0.49%)	2 / 203 (0.99%)	5 / 225 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal dilatation			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	3 / 204 (1.47%)	4 / 203 (1.97%)	7 / 225 (3.11%)
occurrences causally related to treatment / all	1 / 3	1 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 204 (0.00%)	2 / 203 (0.99%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen tongue			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue oedema			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 204 (0.98%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 204 (0.98%)	4 / 203 (1.97%)	10 / 225 (4.44%)
occurrences causally related to treatment / all	1 / 2	1 / 5	1 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			

subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	5 / 225 (2.22%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic necrosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
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			
Rash			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stasis dermatitis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pollakiuria			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyuria			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	3 / 204 (1.47%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal failure acute			

subjects affected / exposed	2 / 204 (0.98%)	3 / 203 (1.48%)	4 / 225 (1.78%)
occurrences causally related to treatment / all	1 / 3	0 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 204 (0.49%)	2 / 203 (0.99%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Flank pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 204 (0.00%)	2 / 203 (0.99%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter infection			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal bacteraemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 204 (0.98%)	2 / 203 (0.99%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	3 / 204 (1.47%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perihepatic abscess			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 204 (1.47%)	2 / 203 (0.99%)	10 / 225 (4.44%)
occurrences causally related to treatment / all	2 / 3	1 / 2	4 / 10
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			

subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	5 / 204 (2.45%)	2 / 203 (0.99%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	2 / 6	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			

subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 204 (0.98%)	3 / 203 (1.48%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 204 (0.98%)	2 / 203 (0.99%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	1 / 3	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	4 / 225 (1.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypokalaemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polydipsia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Everolimus 10 mg/Day	Placebo Comparator	Open-Label Everolimus 10 mg/Day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	201 / 204 (98.53%)	190 / 203 (93.60%)	218 / 225 (96.89%)
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 204 (1.96%)	6 / 203 (2.96%)	12 / 225 (5.33%)
occurrences (all)	4	6	13

Hypertension			
subjects affected / exposed	24 / 204 (11.76%)	9 / 203 (4.43%)	29 / 225 (12.89%)
occurrences (all)	26	10	34
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	35 / 204 (17.16%)	40 / 203 (19.70%)	41 / 225 (18.22%)
occurrences (all)	45	49	59
Chills			
subjects affected / exposed	11 / 204 (5.39%)	1 / 203 (0.49%)	14 / 225 (6.22%)
occurrences (all)	16	2	16
Fatigue			
subjects affected / exposed	91 / 204 (44.61%)	53 / 203 (26.11%)	73 / 225 (32.44%)
occurrences (all)	120	63	95
Influenza like illness			
subjects affected / exposed	9 / 204 (4.41%)	3 / 203 (1.48%)	16 / 225 (7.11%)
occurrences (all)	11	4	21
Oedema peripheral			
subjects affected / exposed	76 / 204 (37.25%)	23 / 203 (11.33%)	66 / 225 (29.33%)
occurrences (all)	98	26	88
Pyrexia			
subjects affected / exposed	56 / 204 (27.45%)	23 / 203 (11.33%)	57 / 225 (25.33%)
occurrences (all)	97	30	109
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 204 (22.06%)	21 / 203 (10.34%)	54 / 225 (24.00%)
occurrences (all)	57	29	76
Dyspnoea			
subjects affected / exposed	33 / 204 (16.18%)	13 / 203 (6.40%)	34 / 225 (15.11%)
occurrences (all)	52	15	41
Epistaxis			
subjects affected / exposed	44 / 204 (21.57%)	3 / 203 (1.48%)	38 / 225 (16.89%)
occurrences (all)	60	3	46
Oropharyngeal pain			
subjects affected / exposed	23 / 204 (11.27%)	12 / 203 (5.91%)	29 / 225 (12.89%)
occurrences (all)	29	17	39
Pleural effusion			

subjects affected / exposed	12 / 204 (5.88%)	2 / 203 (0.99%)	6 / 225 (2.67%)
occurrences (all)	13	2	6
Pneumonitis			
subjects affected / exposed	21 / 204 (10.29%)	0 / 203 (0.00%)	17 / 225 (7.56%)
occurrences (all)	23	0	17
Psychiatric disorders			
Depression			
subjects affected / exposed	14 / 204 (6.86%)	3 / 203 (1.48%)	18 / 225 (8.00%)
occurrences (all)	16	3	19
Insomnia			
subjects affected / exposed	28 / 204 (13.73%)	17 / 203 (8.37%)	27 / 225 (12.00%)
occurrences (all)	30	17	29
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 204 (4.90%)	9 / 203 (4.43%)	17 / 225 (7.56%)
occurrences (all)	12	9	22
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 204 (5.88%)	11 / 203 (5.42%)	28 / 225 (12.44%)
occurrences (all)	13	12	39
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 204 (5.88%)	11 / 203 (5.42%)	25 / 225 (11.11%)
occurrences (all)	13	12	30
Blood creatinine increased			
subjects affected / exposed	10 / 204 (4.90%)	4 / 203 (1.97%)	15 / 225 (6.67%)
occurrences (all)	12	4	26
Haemoglobin decreased			
subjects affected / exposed	15 / 204 (7.35%)	2 / 203 (0.99%)	16 / 225 (7.11%)
occurrences (all)	20	2	21
Weight decreased			
subjects affected / exposed	58 / 204 (28.43%)	24 / 203 (11.82%)	72 / 225 (32.00%)
occurrences (all)	74	25	82
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 204 (11.76%)	16 / 203 (7.88%)	18 / 225 (8.00%)
occurrences (all)	27	17	26
Dysgeusia			

subjects affected / exposed	38 / 204 (18.63%)	11 / 203 (5.42%)	46 / 225 (20.44%)
occurrences (all)	44	11	56
Headache			
subjects affected / exposed	62 / 204 (30.39%)	30 / 203 (14.78%)	52 / 225 (23.11%)
occurrences (all)	87	35	101
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	48 / 204 (23.53%)	18 / 203 (8.87%)	55 / 225 (24.44%)
occurrences (all)	75	19	86
Leukopenia			
subjects affected / exposed	12 / 204 (5.88%)	4 / 203 (1.97%)	9 / 225 (4.00%)
occurrences (all)	24	5	20
Lymphopenia			
subjects affected / exposed	15 / 204 (7.35%)	6 / 203 (2.96%)	10 / 225 (4.44%)
occurrences (all)	27	6	21
Neutropenia			
subjects affected / exposed	14 / 204 (6.86%)	4 / 203 (1.97%)	24 / 225 (10.67%)
occurrences (all)	32	6	35
Thrombocytopenia			
subjects affected / exposed	29 / 204 (14.22%)	2 / 203 (0.99%)	20 / 225 (8.89%)
occurrences (all)	51	2	44
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	18 / 204 (8.82%)	14 / 203 (6.90%)	19 / 225 (8.44%)
occurrences (all)	21	14	19
Abdominal pain			
subjects affected / exposed	47 / 204 (23.04%)	48 / 203 (23.65%)	55 / 225 (24.44%)
occurrences (all)	63	62	72
Abdominal pain upper			
subjects affected / exposed	30 / 204 (14.71%)	15 / 203 (7.39%)	29 / 225 (12.89%)
occurrences (all)	36	18	37
Aphthous stomatitis			
subjects affected / exposed	25 / 204 (12.25%)	8 / 203 (3.94%)	22 / 225 (9.78%)
occurrences (all)	30	9	37
Ascites			

subjects affected / exposed	13 / 204 (6.37%)	4 / 203 (1.97%)	7 / 225 (3.11%)
occurrences (all)	13	4	8
Constipation			
subjects affected / exposed	30 / 204 (14.71%)	26 / 203 (12.81%)	32 / 225 (14.22%)
occurrences (all)	38	30	43
Diarrhoea			
subjects affected / exposed	97 / 204 (47.55%)	47 / 203 (23.15%)	96 / 225 (42.67%)
occurrences (all)	154	64	158
Dry mouth			
subjects affected / exposed	23 / 204 (11.27%)	9 / 203 (4.43%)	8 / 225 (3.56%)
occurrences (all)	24	9	8
Dyspepsia			
subjects affected / exposed	13 / 204 (6.37%)	13 / 203 (6.40%)	8 / 225 (3.56%)
occurrences (all)	13	14	13
Flatulence			
subjects affected / exposed	10 / 204 (4.90%)	8 / 203 (3.94%)	14 / 225 (6.22%)
occurrences (all)	13	8	15
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 204 (2.45%)	6 / 203 (2.96%)	13 / 225 (5.78%)
occurrences (all)	6	6	14
Haemorrhoids			
subjects affected / exposed	6 / 204 (2.94%)	4 / 203 (1.97%)	17 / 225 (7.56%)
occurrences (all)	6	4	17
Mouth ulceration			
subjects affected / exposed	14 / 204 (6.86%)	4 / 203 (1.97%)	15 / 225 (6.67%)
occurrences (all)	36	8	26
Nausea			
subjects affected / exposed	66 / 204 (32.35%)	64 / 203 (31.53%)	80 / 225 (35.56%)
occurrences (all)	89	76	118
Stomatitis			
subjects affected / exposed	110 / 204 (53.92%)	27 / 203 (13.30%)	105 / 225 (46.67%)
occurrences (all)	202	35	223
Toothache			
subjects affected / exposed	11 / 204 (5.39%)	5 / 203 (2.46%)	10 / 225 (4.44%)
occurrences (all)	13	6	11
Vomiting			

subjects affected / exposed	61 / 204 (29.90%)	41 / 203 (20.20%)	70 / 225 (31.11%)
occurrences (all)	89	63	114
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	13 / 204 (6.37%)	5 / 203 (2.46%)	15 / 225 (6.67%)
occurrences (all)	21	9	21
Alopecia			
subjects affected / exposed	8 / 204 (3.92%)	9 / 203 (4.43%)	12 / 225 (5.33%)
occurrences (all)	9	9	12
Dermatitis acneiform			
subjects affected / exposed	9 / 204 (4.41%)	2 / 203 (0.99%)	13 / 225 (5.78%)
occurrences (all)	9	2	18
Dry skin			
subjects affected / exposed	26 / 204 (12.75%)	12 / 203 (5.91%)	28 / 225 (12.44%)
occurrences (all)	29	14	30
Erythema			
subjects affected / exposed	11 / 204 (5.39%)	3 / 203 (1.48%)	4 / 225 (1.78%)
occurrences (all)	13	3	5
Nail disorder			
subjects affected / exposed	28 / 204 (13.73%)	2 / 203 (0.99%)	26 / 225 (11.56%)
occurrences (all)	31	2	30
Onychoclasis			
subjects affected / exposed	14 / 204 (6.86%)	2 / 203 (0.99%)	12 / 225 (5.33%)
occurrences (all)	14	2	14
Pruritus			
subjects affected / exposed	40 / 204 (19.61%)	26 / 203 (12.81%)	42 / 225 (18.67%)
occurrences (all)	44	28	48
Rash			
subjects affected / exposed	107 / 204 (52.45%)	32 / 203 (15.76%)	90 / 225 (40.00%)
occurrences (all)	165	39	136
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	10 / 204 (4.90%)	2 / 203 (0.99%)	13 / 225 (5.78%)
occurrences (all)	13	2	18
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	31 / 204 (15.20%)	14 / 203 (6.90%)	34 / 225 (15.11%)
occurrences (all)	39	19	43
Back pain			
subjects affected / exposed	31 / 204 (15.20%)	22 / 203 (10.84%)	40 / 225 (17.78%)
occurrences (all)	34	25	49
Muscle spasms			
subjects affected / exposed	21 / 204 (10.29%)	8 / 203 (3.94%)	15 / 225 (6.67%)
occurrences (all)	25	11	20
Musculoskeletal chest pain			
subjects affected / exposed	12 / 204 (5.88%)	4 / 203 (1.97%)	15 / 225 (6.67%)
occurrences (all)	15	5	17
Musculoskeletal pain			
subjects affected / exposed	12 / 204 (5.88%)	9 / 203 (4.43%)	17 / 225 (7.56%)
occurrences (all)	13	10	23
Myalgia			
subjects affected / exposed	15 / 204 (7.35%)	14 / 203 (6.90%)	17 / 225 (7.56%)
occurrences (all)	19	21	21
Pain in extremity			
subjects affected / exposed	29 / 204 (14.22%)	10 / 203 (4.93%)	22 / 225 (9.78%)
occurrences (all)	38	10	32
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 204 (1.96%)	3 / 203 (1.48%)	15 / 225 (6.67%)
occurrences (all)	6	5	18
Influenza			
subjects affected / exposed	6 / 204 (2.94%)	7 / 203 (3.45%)	12 / 225 (5.33%)
occurrences (all)	8	8	12
Nasopharyngitis			
subjects affected / exposed	33 / 204 (16.18%)	14 / 203 (6.90%)	38 / 225 (16.89%)
occurrences (all)	62	19	69
Pneumonia			
subjects affected / exposed	11 / 204 (5.39%)	0 / 203 (0.00%)	13 / 225 (5.78%)
occurrences (all)	11	0	18
Sinusitis			

subjects affected / exposed	14 / 204 (6.86%)	4 / 203 (1.97%)	17 / 225 (7.56%)
occurrences (all)	15	4	30
Upper respiratory tract infection			
subjects affected / exposed	16 / 204 (7.84%)	7 / 203 (3.45%)	28 / 225 (12.44%)
occurrences (all)	19	10	46
Urinary tract infection			
subjects affected / exposed	23 / 204 (11.27%)	11 / 203 (5.42%)	23 / 225 (10.22%)
occurrences (all)	29	14	40
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	59 / 204 (28.92%)	37 / 203 (18.23%)	64 / 225 (28.44%)
occurrences (all)	81	42	87
Dehydration			
subjects affected / exposed	10 / 204 (4.90%)	7 / 203 (3.45%)	22 / 225 (9.78%)
occurrences (all)	10	7	25
Diabetes mellitus			
subjects affected / exposed	20 / 204 (9.80%)	0 / 203 (0.00%)	21 / 225 (9.33%)
occurrences (all)	26	0	21
Hypercholesterolaemia			
subjects affected / exposed	26 / 204 (12.75%)	2 / 203 (0.99%)	16 / 225 (7.11%)
occurrences (all)	26	2	16
Hyperglycaemia			
subjects affected / exposed	40 / 204 (19.61%)	21 / 203 (10.34%)	58 / 225 (25.78%)
occurrences (all)	57	41	79
Hyperlipidaemia			
subjects affected / exposed	16 / 204 (7.84%)	2 / 203 (0.99%)	10 / 225 (4.44%)
occurrences (all)	18	2	10
Hypoglycaemia			
subjects affected / exposed	11 / 204 (5.39%)	7 / 203 (3.45%)	10 / 225 (4.44%)
occurrences (all)	14	7	16
Hypokalaemia			
subjects affected / exposed	17 / 204 (8.33%)	5 / 203 (2.46%)	11 / 225 (4.89%)
occurrences (all)	21	5	19
Hypophosphataemia			
subjects affected / exposed	20 / 204 (9.80%)	3 / 203 (1.48%)	21 / 225 (9.33%)
occurrences (all)	32	3	31

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2010	The amendment included the following: 1. Data source for the primary endpoint was changed from progression-free survival by central radiology review to progression-free survival (PFS) by investigator (local radiology) review. The analysis of primary endpoint by central radiology was still to be performed and reported as supportive analysis. 2. Progression-free survival discrepancies between local and central radiology were adjudicated by a radiologist and an oncologist, both experts in NETs, while maintaining the independent and blinding of the central review process. 3. Cancelling of interim analysis 4. Redefinition of hierarchical testing procedure and timing of the final OS analysis (key secondary endpoint). The primary comparison of the overall response rate between the treatment arms was performed in the ITT population and based on local investigator data. Supportive analysis was performed using data from local adjudicated central radiology review. 5. Updated standard safety language for RAD001 to include update on hepatitis B and C infections, managing hyperglycemia, pneumonitis, duration of adequate contraceptive use after end of treatment, removal of collecting pregnant partner data, use of CYP450 3Ar or Pgp inducers/inhibitors, and timing of RAD001 administration with respect to food intake.

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/CtrdWeb/home.novfor complete trial results.

Notes: