Clinical trial results:
A randomized, double-blind, multi-center phase III study comparing everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in patients with advanced gastric cancer after progression on prior systemic chemotherapy.

Summary

EudraCT number	2008-006544-20
Trial protocol	NL BE DE GB FR IT ES
Global end of trial date	30 January 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	CRAD001R2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00879333
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	30 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival between everolimus (RAD001)+best supportive care (BSC) and placebo+BSC in patients with advanced gastric cancer after progression on prior systemic chemotherapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Best supportive care (BSC) plus placebo was used as the comparator. Best supportive care was in accordance with the local practice of an individual institution or center, and specifically excluded anti-cancer treatments.

Actual start date of recruitment	07 July 2009
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	Spain: 6
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	China: 128
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Japan: 116
Country: Number of subjects enrolled	Korea, Republic of: 77
Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Australia: 54
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Peru: 11

Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	656
EEA total number of subjects	157

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)	389
From 65 to 84 years	261
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Six hundred and fifty-six patients with advanced gastric cancer (AGC) who had progressed after one or two prior lines of systemic chemotherapy were randomized to receive either everolimus or placebo.

Pre-assignment

Screening details:

Adult patients with histologically or cytologically confirmed AGC which progressed after 1 or 2 prior systemic chemotherapy lines were enrolled in the study, stratified by both number of prior chemotherapy lines for advanced disease (1 line vs 2 lines) and region (Asia vs ROW). Intended samples size was 633, with 656 randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus + BSC

Arm description:

All patients were randomized to receive everolimus (RAD001) + best supportive care (BSC). All patients took two 5 mg tablets orally of everolimus once daily. Therefore, all patients in the everolimus arm took a total daily dose of 10 mg. Best supportive care was in accordance with the local practice of an individual institution or center, and specifically excluded anti-cancer treatments.

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

Dosage and administration details:

All patients took two 5 mg tablets of everolimus orally once daily. Therefore, all patients in the everolimus arm took a total daily dose of 10 mg.

Arm title	Placebo + BSC

Arm description:

All patients were randomized to receive placebo + BSC. All patients took two 5 mg tablets orally of matching placebo once daily. Therefore, all patients in the placebo receive matching tablets of total daily dose of 10 mg. Best supportive care was in accordance with the local practice of an individual institution or center, and specifically excluded anticancer treatments.

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

Dosage and administration details:

All patients took two 5 mg tablets of matching placebo orally once daily. Therefore, all patients in the placebo arm received matching tablets of a total daily dose of 10 mg.

Number of subjects in period 1	Everolimus + BSC	Placebo + BSC
Started	439	217
Completed	11	0
Not completed	428	217
Adverse event, serious fatal	16	5
Abnormal Laboratory	1	-
Adverse event, non-fatal	94	34
Withdrawal by Subject	20	7
Administrative Problems	2	-
Protocol Violation	1	1
Lost to follow-up	2	1
Disease Progression	292	169

Baseline characteristics

Reporting groups	
5HSRUWLQJ JURXS WLWOH	(YHUROLPXV %6&
5HSRUWLQJ JURXS GHVFULSWLRQ	
$OO SDWLHQWV ZHUH UDQGRPL]HG WR UHFHLYH HYHUROLPXV 5$' EHVW VX WRRN WZR PJ WDEOHWV RUDOO\ RI HYHUROLPXV RQFH GDLO\ 7KHUHIRUH DO D WRWDO GDLO\ GRVH RI PJ %HVW VXSSRUWLYH FDUH ZDV LQ DFFRUGDQFH LQGLYLGXDO LQVWLWXWLRQ RU FHQWHU DQG VSHFLILFDOO\ H[FOXGHG DQWL R	
5HSRUWLQJ JURXS WLWOH	3ODFHER %6&
5HSRUWLQJ JURXS GHVFULSWLRQ	
$OO SDWLHQWV ZHUH UDQGRPL]HG WR UHFHLYH SODFHER %6& $OO SDWLHQW PDWFKLQJ SODFHER RQFH GDLO\ 7KHUHIRUH DOO SDWLHQWV LQ WKH SODFHE GRVH RI PJ %HVW VXSSRUWLYH FDUH ZDV LQ DFFRUGDQFH ZLWK WKH ORFDO RU FHQWHU DQG VSHFLILFDOO\ H[FOXGHG DQWLFDQFHU WUHDWPHQWV	

Reporting group values	(YHUROLPXV	%36&DFHER	%6&	7RWDO
1XPEHU RI VXEMHFWV				
$JH FDWHJRULFDO 8QLWV 6XEMHFWV				
\HDUV ! \HDUV				
$JH FRQWLQXRXV				
7KH (0$ UHVXOW V\VWHP DXWRSRSXODWHV WKH ³ ³ DQG ZLOO QRW DOORZ WKH ZKLFK LV VWDQGDUG GHYLDWLRQ				
8QLWV \HDUV DULWKPHWLF PHDQ VWDQGDUG GHYLDWLRQ	“	“		
*HQGHU FDWHJRULFDO 8QLWV 6XEMHFWV				
)HPDOH 0DOH				
5DFH (WKQLFLW\ 8QLWV 6XEMHFWV				
&DXFDVLDQ %ODFN $VLDQ 1DWLYH $PHULFDQ 2WKHU				

End points

End points reporting groups

Reporting group title	Everolimus + BSC

Reporting group description:

All patients were randomized to receive everolimus (RAD001) + best supportive care (BSC). All patients took two 5 mg tablets orally of everolimus once daily. Therefore, all patients in the everolimus arm took a total daily dose of 10 mg. Best supportive care was in accordance with the local practice of an individual institution or center, and specifically excluded anti-cancer treatments.

Reporting group title	Placebo + BSC

Reporting group description:

All patients were randomized to receive placebo + BSC. All patients took two 5 mg tablets orally of matching placebo once daily. Therefore, all patients in the placebo receive matching tablets of total daily dose of 10 mg. Best supportive care was in accordance with the local practice of an individual institution or center, and specifically excluded anticancer treatments.

Primary: Overall Survival

End point title	Overall Survival

End point description:

The primary objective of this study was to compare OS between everolimus + best supportive care (BSC) and placebo + BSC. OS, was defined as the time from date of randomization to the date of death due to any cause. If at the analysis cut-off date a patient was not known to have died, survival was censored at the date of the last contact. OS was analyzed using the Kaplan Meier estimates method. The Full Analysis Set (FAS) was used.

End point type	Primary

End point timeframe:

2.5 years

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	217		
Units: Months				
median (confidence interval 95%)				
Median Overall Survival (Months)	5.39 (4.8 to 6.01)	4.34 (3.81 to 5.49)		

Statistical analyses

Statistical analysis title	Analysis of overall survival using K-M and Cox PH

Statistical analysis description:

The primary analysis was a comparison of OS between the treatment groups in the FAS. The statistical hypotheses were: H0: SEverolimus(t) = SPlacebo(t) vs H1: SEverolimus(t) > SPlacebo(t), where SEverolimus(t) and SPlacebo(t) are the survival functions in everolimus + BSC and placebo + BSC groups, respectively. The null hypothesis was tested with the one-sided log-rank test using an overall type I error rate of 2.5%. Two-sided 95% CI was estimated from a Cox proportional hazard model.

Comparison groups	Everolimus + BSC v Placebo + BSC

Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1244 [1]
Method	Kaplan-Meier method and Cox PH model

Notes:

[1] - one-sided stratified log-rank test p-value

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression free survival is defined as time from the date of randomization to the date of the first documented disease progression or death due to any cause where progression was based on Investigator assessment of baseline and post-baseline scans according to RECIST. Progression free survival was censored if no PFS event was observed before the first to occur out of (i) the cut-off date, or (ii) the date when a further anticancer therapy was started. The censoring date was the date of the last adequate tumor assessment before either of these two events occurred. If a PFS event was observed after two or more missing or non-evaluable tumor assessments, then the date of progression was censored at the date of the last adequate tumor assessment; for a PFS event observed after a single missing or non-evaluable tumor assessment, the actual date of disease progression was used. Anslsis was done using Kaplan-Meier estimates method.

End point type	Secondary

End point timeframe:

2.5 years

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	217		
Units: Months				
median (confidence interval 95%)				
Progression Free Survival (months)	1.68 (1.51 to 1.94)	1.41 (1.38 to 1.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome: Time to definitive deterioration of EORTC QLQ-C30 scores

End point title	Patient Reported Outcome: Time to definitive deterioration of EORTC QLQ-C30 scores

End point description:

The EORTC QLQ-C30 global health status/quality of life sub-scale (QL) was pre-specified as the primary domain of interest, followed by physical functioning (PF), social functioning (SF) and emotional functioning (EF). The EORTC QLQ-C30 questionnaire, along with a module specific for gastric cancer patients (EORTC QLQ-STO22), was used to evaluate patient-reported outcome (PRO). The QLQ-C30 has five function scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting) and a global health status/quality of life scale. In addition, there are questions that assess specific symptoms. The QLQ-STO22 consists of 22 questions that make up five multi-item scales (dysphagia, pain, reflux, eating and anxiety) and four single-item scales (dry mouth, tasting,

body image and hair loss).

End point type	Secondary

End point timeframe:

2.5 years

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	217		
Units: Months				
median (confidence interval 95%)				
In QL score by at least 5 %	1.51 (1.28 to 1.84)	1.45 (1.05 to 1.68)		
In PF score by at least 5 %	1.35 (1.12 to 1.54)	1.15 (1.02 to 1.64)		
In SF score by at least 5 %	1.87 (1.84 to 2.3)	1.87 (1.64 to 2.46)		
In EF score by at least 5 %	1.84 (1.61 to 2.1)	1.71 (1.41 to 1.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of Eastern Cooperative Oncology Group Performance Status

End point title	Time to definitive deterioration of Eastern Cooperative Oncology Group Performance Status

End point description:

The ECOG PS scale was used to classify patients according to their functional impairment, with scores ranging from 0 (fully active) to 5 (dead). An analysis of the time to definitive deterioration of the ECOG PS by one category of the score from baseline was performed. Definitive deterioration was defined as a definitive increase by one category from baseline in ECOG PS, with no later improvements observed during the course of the study. A single measure reporting an increase in ECOG PS is sufficient to consider it as a definitive worsening only if it was the last one available for the patient. Kaplan-Meier method was used to estimate the distribution function of time to definitive worsening.

End point type	Secondary

End point timeframe:

2.5 years

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	217		
Units: Months				
median (confidence interval 95%)				
Time to definitive deterioration of ECOG PS Score	2.3 (1.97 to 2.79)	2.23 (1.87 to 2.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall response rate (ORR) was defined as the proportion of patients with measurable disease in whom best overall response (OR) was either complete response (CR) or partial response (PR) according to RECIST criteria.

End point type	Secondary

End point timeframe:

2.5 years

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	217		
Units: Participants				
number (not applicable)				
Measurable Disease	379	191		
Complete Response (CR)	1	0		
Partial Response (PR)	16	4		
Overall Response Rate (ORR)	17	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus steady state concentrations at predose (Cmin) and Cmax at Week 5

End point title	Everolimus steady state concentrations at predose (Cmin) and Cmax at Week 5

End point description:

Cmin is the minimum (trough) steady-state drug concentration in the blood during multiple dosing and Cmax is the maximum (peak) blood drug concentration after dose administration. Cmax is estimated as the maximum of C1h and C2H. C1h is 1 hour post-dose blood concentration and C2h is 2 hour post-dose blood concentration. Only valid pre-dose (Cmin), C1h, and C2h everolimus samples were included in the analysis. Valid pre-dose samples were confirmed blood samples collected at steady-state, collected immediately prior to dosing on the same study day, and collected at approximately 24 ± 4 hours after the previous dose and with no vomiting within the first 4 hours following the last dose. Valid C1h and C2h samples were confirmed blood samples collected at steady-state and within ± 1 hour window and with no vomiting within the first 4 hours following the current and previous dose.

End point type	Secondary

End point timeframe:

Week 5

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218[2]	18[3]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose (Cmin) (n: 201,18)	16.143 (± 10.7723)	10.498 (± 6.1432)		
Cmax (n: 218,16)	72.775 (± 36.5435)	37.269 (± 27.2086)		

Notes:

[2] - All PK analyses were based on the safety population in patients with evaluable samples.

[3] - All PK analyses were based on the safety population in patients with evaluable samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus steady state concentrations at predose (Cmin) and Cmax by region Asia vs. rest of world

End point title	Everolimus steady state concentrations at predose (Cmin) and Cmax by region Asia vs. rest of world

End point description:

Cmin is the minimum (trough) steady-state drug concentration in the blood during multiple dosing and Cmax is the maximum (peak) blood drug concentration after dose administration. Cmax is estimated as the maximum of C1h and C2H. C1h is 1 hour post-dose blood concentration and C2h is 2 hour post-dose blood concentration. Only valid pre-dose (Cmin), C1h, and C2h everolimus samples were included in the analysis. Valid pre-dose samples were confirmed blood samples collected at steady-state, collected immediately prior to dosing on the same study day, and collected at approximately 24 ± 4 hours after the previous dose and with no vomiting within the first 4 hours following the last dose. Valid C1h and C2h samples were confirmed blood samples collected at steady-state and within ± 1 hour window and with no vomiting within the first 4 hours following the current and previous dose.

End point type	Secondary

End point timeframe:

Week 5

End point values	Everolimus + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218[4]	18[5]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Asia: Pre-dose (n:127, 11)	16.804 (± 9.6163)	9.921 (± 5.1565)		
Asia: Cmax (n:132, 10)	73.568 (± 34.1898)	34.58 (± 26.811)		

Rest of World: Pre-dose (n=74, 7)	15.009 (± 12.5)	11.406 (± 7.8128)		
Rest of World: Cmax (n=86, 6)	71.558 (± 40.0655)	41.75 (± 29.8074)		

Notes:

[4] - All PK analyses were based on the safety population in patients with evaluable samples.

[5] - All PK analyses were based on the safety population in patients with evaluable samples.

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	RAD001 plus best supportive care

Reporting group description:

RAD001 plus best supportive care

Reporting group title	Placebo plus best supportive care

Reporting group description:

Placebo plus best supportive care

Serious adverse events	RAD001 plus best supportive care	Placebo plus best supportive care	
Total subjects affected by serious adverse events			
subjects affected / exposed	210 / 437 (48.05%)	89 / 215 (41.40%)	
number of deaths (all causes)	88	49	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	3 / 437 (0.69%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pallor			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	12 / 437 (2.75%)	6 / 215 (2.79%)	
occurrences causally related to treatment / all	4 / 12	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	8 / 437 (1.83%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	3 / 8	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	14 / 437 (3.20%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	4 / 16	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 437 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	10 / 437 (2.29%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	6 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent malfunction			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	9 / 437 (2.06%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	2 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 437 (0.46%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	9 / 437 (2.06%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Productive cough			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 437 (0.46%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			

Blood creatinine increased			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Colon injury			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic rupture			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal injury			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Depressed level of consciousness			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 437 (0.23%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 437 (3.43%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	5 / 15	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			

subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 437 (0.92%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal adhesions			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal compartment syndrome			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 437 (0.46%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	21 / 437 (4.81%)	12 / 215 (5.58%)	
occurrences causally related to treatment / all	6 / 22	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 437 (0.46%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal rigidity			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	9 / 437 (2.06%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastrointestinal bleeding			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 437 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 437 (1.37%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	3 / 437 (0.69%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	5 / 437 (1.14%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	1 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			

subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	2 / 437 (0.46%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stenosis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	13 / 437 (2.97%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	5 / 14	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			

subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 437 (0.46%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	5 / 437 (1.14%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal hernia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	5 / 437 (1.14%)	5 / 215 (2.33%)	
occurrences causally related to treatment / all	0 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 437 (0.23%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	9 / 437 (2.06%)	9 / 215 (4.19%)	
occurrences causally related to treatment / all	3 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	2 / 437 (0.46%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal adhesions			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal disorder			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal obstruction			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 437 (0.00%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 437 (0.69%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 437 (0.46%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	14 / 437 (3.20%)	10 / 215 (4.65%)	
occurrences causally related to treatment / all	6 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	2 / 437 (0.46%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	4 / 437 (0.92%)	5 / 215 (2.33%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 437 (0.23%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			

subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	5 / 437 (1.14%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	2 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Acinetobacter infection			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric infection			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 437 (0.69%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	2 / 437 (0.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 437 (2.75%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	4 / 12	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 437 (0.46%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	4 / 437 (0.92%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Skin infection			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	4 / 437 (0.92%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 437 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	21 / 437 (4.81%)	8 / 215 (3.72%)	
occurrences causally related to treatment / all	6 / 21	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 437 (0.69%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			
subjects affected / exposed	0 / 437 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid intake reduced			

subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 437 (0.23%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 437 (0.23%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RAD001 plus best supportive care	Placebo plus best supportive care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	416 / 437 (95.19%)	193 / 215 (89.77%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	28 / 437 (6.41%)	9 / 215 (4.19%)	
occurrences (all)	29	9	
Aspartate aminotransferase increased			
subjects affected / exposed	34 / 437 (7.78%)	8 / 215 (3.72%)	
occurrences (all)	35	8	
Blood alkaline phosphatase increased			
subjects affected / exposed	34 / 437 (7.78%)	6 / 215 (2.79%)	
occurrences (all)	36	7	
Weight decreased			
subjects affected / exposed	87 / 437 (19.91%)	19 / 215 (8.84%)	
occurrences (all)	92	19	
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 437 (5.03%)	12 / 215 (5.58%)	
occurrences (all)	27	12	
Dysgeusia			
subjects affected / exposed	26 / 437 (5.95%)	7 / 215 (3.26%)	
occurrences (all)	29	8	
Headache			
subjects affected / exposed	32 / 437 (7.32%)	8 / 215 (3.72%)	
occurrences (all)	37	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	108 / 437 (24.71%)	42 / 215 (19.53%)	
occurrences (all)	135	47	
Leukopenia			
subjects affected / exposed	30 / 437 (6.86%)	3 / 215 (1.40%)	
occurrences (all)	38	3	
Neutropenia			

subjects affected / exposed	47 / 437 (10.76%)	6 / 215 (2.79%)	
occurrences (all)	65	6	
Thrombocytopenia			
subjects affected / exposed	77 / 437 (17.62%)	4 / 215 (1.86%)	
occurrences (all)	93	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	67 / 437 (15.33%)	18 / 215 (8.37%)	
occurrences (all)	72	19	
Fatigue			
subjects affected / exposed	146 / 437 (33.41%)	63 / 215 (29.30%)	
occurrences (all)	169	68	
Oedema peripheral			
subjects affected / exposed	49 / 437 (11.21%)	21 / 215 (9.77%)	
occurrences (all)	53	23	
Pyrexia			
subjects affected / exposed	77 / 437 (17.62%)	24 / 215 (11.16%)	
occurrences (all)	108	35	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	39 / 437 (8.92%)	20 / 215 (9.30%)	
occurrences (all)	39	21	
Abdominal pain			
subjects affected / exposed	90 / 437 (20.59%)	49 / 215 (22.79%)	
occurrences (all)	105	51	
Abdominal pain upper			
subjects affected / exposed	51 / 437 (11.67%)	26 / 215 (12.09%)	
occurrences (all)	59	30	
Constipation			
subjects affected / exposed	92 / 437 (21.05%)	41 / 215 (19.07%)	
occurrences (all)	101	45	
Diarrhoea			
subjects affected / exposed	112 / 437 (25.63%)	33 / 215 (15.35%)	
occurrences (all)	159	37	
Dyspepsia			

subjects affected / exposed	22 / 437 (5.03%)	8 / 215 (3.72%)	
occurrences (all)	24	8	
Nausea			
subjects affected / exposed	129 / 437 (29.52%)	63 / 215 (29.30%)	
occurrences (all)	147	76	
Stomatitis			
subjects affected / exposed	173 / 437 (39.59%)	22 / 215 (10.23%)	
occurrences (all)	241	26	
Vomiting			
subjects affected / exposed	98 / 437 (22.43%)	54 / 215 (25.12%)	
occurrences (all)	125	70	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	50 / 437 (11.44%)	17 / 215 (7.91%)	
occurrences (all)	57	18	
Dyspnoea			
subjects affected / exposed	54 / 437 (12.36%)	21 / 215 (9.77%)	
occurrences (all)	59	21	
Epistaxis			
subjects affected / exposed	29 / 437 (6.64%)	1 / 215 (0.47%)	
occurrences (all)	32	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	23 / 437 (5.26%)	7 / 215 (3.26%)	
occurrences (all)	27	7	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	22 / 437 (5.03%)	2 / 215 (0.93%)	
occurrences (all)	23	2	
Pruritus			
subjects affected / exposed	47 / 437 (10.76%)	9 / 215 (4.19%)	
occurrences (all)	54	9	
Rash			
subjects affected / exposed	86 / 437 (19.68%)	19 / 215 (8.84%)	
occurrences (all)	110	21	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	51 / 437 (11.67%)	22 / 215 (10.23%)	
occurrences (all)	57	23	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	24 / 437 (5.49%)	5 / 215 (2.33%)	
occurrences (all)	28	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	46 / 437 (10.53%)	16 / 215 (7.44%)	
occurrences (all)	52	16	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	202 / 437 (46.22%)	76 / 215 (35.35%)	
occurrences (all)	235	82	
Hyperglycaemia			
subjects affected / exposed	31 / 437 (7.09%)	6 / 215 (2.79%)	
occurrences (all)	40	6	
Hypoalbuminaemia			
subjects affected / exposed	25 / 437 (5.72%)	12 / 215 (5.58%)	
occurrences (all)	26	13	
Hypokalaemia			
subjects affected / exposed	52 / 437 (11.90%)	9 / 215 (4.19%)	
occurrences (all)	61	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2010	Clarifications to GEJ tumor language added, removal of amylase and lipase levels as an inclusion criterion, permitting enrollment of patients with grade 2 neuropathy, adding exclusion for patients with prior malignancies, removal of pulmonary function testing at screening, amending the pulmonary exclusion criterion, patients who were enterally fed were not eligible, and patients qualified for the study based on local laboratory results. Guidance provided for identification of patients at risk for hepatitis B, that include providing prophylactic treatment to them prior to and throughout everolimus therapy, monitoring them for reactivation of HBV, and management of patients at risk of hepatitis C viral reactivation. Guidance provided for management of hyperglycemia and duration of use of adequate contraception after end of trial therapy. Guidance provided regarding use of CYP3A4 and/or PgP inducers and inhibitors as modified with the Internal Clinical Pharmacology Drug-drug interaction memo; language modified regarding the administration of everolimus after meals; planned IDMC outputs excluded PK data; instead to receive unblinded safety data by prior gastrectomy (y/n); added separate exploratory Cox model on the sub-set of distal gastric tumor patients.

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.

Four randomized patients, 2 patients each from the everolimus and placebo arms were excluded from the safety analyses as they did not receive any dose of study treatment. This study did not meet its primary objective.

Notes: