Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter Phase III study of RAD001 adjuvant therapy in high risk patients with Diffuse Large B-Cell Lymphoma (DLBCL) of RAD001 versus matching placebo after patients have achieved complete response with first-line rituximab-chemotherapy

Summary

EudraCT number	2008-000498-40
Trial protocol	CZ HU SK AT IT DE GR ES
Global end of trial date	15 June 2016

Results information

Result version number	v1 (current)
This version publication date	30 June 2017
First version publication date	30 June 2017

Trial information

Trial identification

Sponsor protocol code	CRAD001N2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00790036
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	15 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of everolimus versus matching placebo measured as disease free survival (DFS) in high risk patients with DLBCL after achieving complete response (CR) following first-line R-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: -

Actual start date of recruitment	24 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	Argentina: 10
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Canada: 48
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	China: 72
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Egypt: 16
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Japan: 81

Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Lebanon: 17
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	Saudi Arabia: 4
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Thailand: 16
Country: Number of subjects enrolled	Turkey: 18
Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 1
Worldwide total number of subjects	742
EEA total number of subjects	224

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)	393
From 65 to 84 years	347
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Considering a recruitment period of 53 months and a final primary analysis performed after an anticipated duration of 69 months after study start, 727 patients had to be included. Actual enrolled: 742.

Pre-assignment

Screening details:

This was a randomized, double-blind, placebo-controlled, multicenter Phase III study in high risk patients (IPI 3-5) who achieved CR after first-line R-chemotherapy treatment.

Period 1

Period 1 title	Overall Study (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	RAD001 (Everolimus)

Arm description:

RAD001 10 mg (two 5 mg tablets), daily for 12 months

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

Dosage and administration details:

Everolimus was formulated as tablets of 5 mg strength,
blister-packed under aluminum foil in units of 10 tablets. Everolimus was dispensed on Day 1 of each cycle until the end-of-treatment visit.

Arm title	Placebo

Arm description:

Everolimus placebo 10 mg (two 5 mg tablets), daily for 12 months

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:

Matching placebo was formulated as tablets of 5 mg strength,
blister-packed under aluminum foil in units of 10 tablets. Matching placebo was dispensed on Day 1 of each cycle until the end-of-treatment visit.

Number of subjects in period 1	RAD001 (Everolimus)	Placebo
Started	372	370
Untreated participants	4 [1]	6 [2]
Completed	177	249
Not completed	195	121
Adverse event, serious fatal	1	-
Consent withdrawn by subject	18	7
Disease progression	24	48
Adverse event, non-fatal	113	44
Administrative problems	5	9
Abnormal lab values	3	2
Lost to follow-up	1	2
Subject/guardian decision	20	7
Protocol deviation	10	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These subjects, although randomized, were not treated with study drug due to administrative problems, protocol deviation and subject withdrawal of consent.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These subjects, although randomized, were not treated with study drug due to administrative problems and subject withdrawal of consent.

Baseline characteristics

Reporting groups	
Reporting group title	RAD001 (Everolimus)
Reporting group description:	
RAD001 10 mg (two 5 mg tablets), daily for 12 months	
Reporting group title	Placebo
Reporting group description:	
Everolimus placebo 10 mg (two 5 mg tablets), daily for 12 months	

Reporting group values	RAD001 (Everolimus)	Placebo	Total
Number of subjects	372	370	742
Age categorical Units: Subjects			
Adults (18-64 years)	192	201	393
From 65-84 years	180	167	347
85 years and over	0	2	2
Age Continuous Units: Years			
arithmetic mean	60.6	60.9	
standard deviation	± 13.72	± 13.61	-
Gender, Male/Female Units: Subjects			
Female	204	166	370
Male	168	204	372

End points

End points reporting groups	
Reporting group title	RAD001 (Everolimus)
Reporting group description: RAD001 10 mg (two 5 mg tablets), daily for 12 months	
Reporting group title	Placebo
Reporting group description: Everolimus placebo 10 mg (two 5 mg tablets), daily for 12 months	

Primary: Disease-free Survival (DFS)	
End point title	Disease-free Survival (DFS)
End point description: DFS was defined as the time from date of randomization to the date of event defined as the first documented relapse of the disease or death due to any cause. Relapse was based on investigator assessment and was assigned only if: It was documented according to Cheson guidelines by an objective radiological assessment method; It was documented by a biopsy proven lymphoma including new or recurrent bone marrow involvement; A new anticancer therapy for lymphoma started with subsequent confirmation of the relapse within 4 weeks of the start of this anticancer therapy	
End point type	Primary
End point timeframe: From date of randomization to the date of event defined as the first documented recurrence of the disease, or death due to any cause and up to 6 years	

End point values	RAD001 (Everolimus)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	372	370		
Units: Percentage of participants				
number (confidence interval 95%)	77.8 (72.7 to 82.1)	77 (72.1 to 81.1)		

Statistical analyses

Statistical analysis title	DFS statistical analysis
Comparison groups	RAD001 (Everolimus) v Placebo
Number of subjects included in analysis	742
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.22

Notes:

[1] - P-value was obtained from the one-sided unstratified log rank test.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from date of randomization to date of death due to any cause. If the patient was not known to have died, survival was censored at the date of the last contact.

End point type	Secondary

End point timeframe:

From date of randomization to date of death due to any cause up to around 7 years

End point values	RAD001 (Everolimus)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	372	370		
Units: Percentage of participants				
number (confidence interval 95%)				
2 years	90.7 (87 to 93.4)	88.3 (84.4 to 91.3)		
3 years	88 (83.8 to 91.1)	83.7 (79.3 to 87.3)		
4 years	85.4 (80.7 to 89.1)	80.7 (75.8 to 84.7)		
5 years	83.4 (78.1 to 87.5)	77.4 (71.7 to 82)		
6 years	80.3 (71.6 to 86.6)	77.4 (71.7 to 82)		

Statistical analyses

Statistical analysis title	OS Statistical analysis
Comparison groups	RAD001 (Everolimus) v Placebo
Number of subjects included in analysis	742
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.09

Secondary: Lymphoma-specific survival (LSS)	
End point title	Lymphoma-specific survival (LSS)
End point description: LSS was defined as time from randomization to death as a result of lymphoma.	
End point type	Secondary
End point timeframe: From randomization to death documented as a result of lymphoma up to 7 years	

End point values	RAD001 (Everolimus)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	372	370		
Units: Percentage of participants				
number (confidence interval 95%)				
2 years	94.9 (91.8 to 96.8)	90.5 (86.9 to 93.2)		
3 years	93.1 (89.6 to 95.5)	88.8 (84.9 to 91.8)		
4 years	91.6 (87.6 to 94.3)	86.9 (82.6 to 90.3)		
5 years	89.4 (84.6 to 92.8)	85.4 (80.5 to 89.2)		
6 years	89.4 (84.6 to 92.8)	85.4 (80.5 to 89.2)		

Statistical analyses

Statistical analysis title	LSS Statistical analysis
Comparison groups	RAD001 (Everolimus) v Placebo
Number of subjects included in analysis	742
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.07

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	19.0

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	All Patients

Reporting group description:

All Patients

Serious adverse events	Everolimus	Placebo	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	105 / 368 (28.53%)	62 / 364 (17.03%)	167 / 732 (22.81%)
number of deaths (all causes)	5	2	7
number of deaths resulting from adverse events	2	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 368 (0.00%)	2 / 364 (0.55%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythromelalgia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose ulceration			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vein disorder			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	3 / 368 (0.82%)	2 / 364 (0.55%)	5 / 732 (0.68%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular swelling			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 368 (0.82%)	2 / 364 (0.55%)	5 / 732 (0.68%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulomatous pneumonitis			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperventilation			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obliterative bronchiolitis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	4 / 368 (1.09%)	1 / 364 (0.27%)	5 / 732 (0.68%)
occurrences causally related to treatment / all	4 / 4	1 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 368 (0.82%)	0 / 364 (0.00%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis allergic			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device difficult to use			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 368 (0.27%)	1 / 364 (0.27%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biopsy lung			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood bilirubin increased			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood cholesterol increased			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CD4 lymphocytes decreased			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 368 (0.82%)	0 / 364 (0.00%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	4 / 4	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 368 (0.27%)	3 / 364 (0.82%)	4 / 732 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femoral neck fracture			
subjects affected / exposed	0 / 368 (0.00%)	2 / 364 (0.55%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital haematoma			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 368 (0.27%)	2 / 364 (0.55%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	4 / 368 (1.09%)	2 / 364 (0.55%)	6 / 732 (0.82%)
occurrences causally related to treatment / all	1 / 4	1 / 3	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	5 / 368 (1.36%)	1 / 364 (0.27%)	6 / 732 (0.82%)
occurrences causally related to treatment / all	1 / 5	0 / 1	1 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiogenic shock			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	1 / 368 (0.27%)	1 / 364 (0.27%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brachial plexopathy			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery occlusion			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalomalacia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Headache			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IVth nerve paresis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 368 (0.00%)	2 / 364 (0.55%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular dementia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paresis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	8 / 368 (2.17%)	5 / 364 (1.37%)	13 / 732 (1.78%)
occurrences causally related to treatment / all	8 / 8	3 / 5	11 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			

subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	7 / 368 (1.90%)	4 / 364 (1.10%)	11 / 732 (1.50%)
occurrences causally related to treatment / all	6 / 7	4 / 4	10 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 368 (0.00%)	3 / 364 (0.82%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmoplegia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			

subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth ulceration			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 368 (0.27%)	1 / 364 (0.27%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	2 / 2	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
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 function abnormal			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
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			
Dermatitis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pityriasis rosea			

subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myopathy			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 368 (0.27%)	1 / 364 (0.27%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 368 (0.27%)	1 / 364 (0.27%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus colitis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 368 (0.27%)	2 / 364 (0.55%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	1 / 1	2 / 2	3 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Herpes zoster			
subjects affected / exposed	1 / 368 (0.27%)	1 / 364 (0.27%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Moraxella infection			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	3 / 368 (0.82%)	1 / 364 (0.27%)	4 / 732 (0.55%)
occurrences causally related to treatment / all	3 / 3	0 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 368 (1.90%)	3 / 364 (0.82%)	10 / 732 (1.37%)
occurrences causally related to treatment / all	6 / 7	2 / 3	8 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cryptococcal			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyonephrosis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 368 (0.54%)	0 / 364 (0.00%)	2 / 732 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Skin infection			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tinea pedis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 368 (0.27%)	3 / 364 (0.82%)	4 / 732 (0.55%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 368 (0.54%)	1 / 364 (0.27%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 364 (0.27%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipidaemia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	3 / 368 (0.82%)	0 / 364 (0.00%)	3 / 732 (0.41%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 364 (0.00%)	1 / 732 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
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	Placebo	All Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	348 / 368 (94.57%)	276 / 364 (75.82%)	624 / 732 (85.25%)
Investigations			
Blood cholesterol increased			
subjects affected / exposed	21 / 368 (5.71%)	5 / 364 (1.37%)	26 / 732 (3.55%)
occurrences (all)	26	7	33
Blood lactate dehydrogenase increased			
subjects affected / exposed	33 / 368 (8.97%)	5 / 364 (1.37%)	38 / 732 (5.19%)
occurrences (all)	41	6	47
CD4 lymphocytes decreased			
subjects affected / exposed	37 / 368 (10.05%)	18 / 364 (4.95%)	55 / 732 (7.51%)
occurrences (all)	41	21	62
Weight decreased			
subjects affected / exposed	28 / 368 (7.61%)	6 / 364 (1.65%)	34 / 732 (4.64%)
occurrences (all)	30	6	36
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 368 (5.16%)	13 / 364 (3.57%)	32 / 732 (4.37%)
occurrences (all)	20	15	35
Nervous system disorders			

Dizziness			
subjects affected / exposed	21 / 368 (5.71%)	27 / 364 (7.42%)	48 / 732 (6.56%)
occurrences (all)	22	32	54
Dysgeusia			
subjects affected / exposed	25 / 368 (6.79%)	7 / 364 (1.92%)	32 / 732 (4.37%)
occurrences (all)	28	7	35
Headache			
subjects affected / exposed	42 / 368 (11.41%)	31 / 364 (8.52%)	73 / 732 (9.97%)
occurrences (all)	50	34	84
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 368 (16.58%)	18 / 364 (4.95%)	79 / 732 (10.79%)
occurrences (all)	70	23	93
Leukopenia			
subjects affected / exposed	29 / 368 (7.88%)	23 / 364 (6.32%)	52 / 732 (7.10%)
occurrences (all)	50	27	77
Lymphopenia			
subjects affected / exposed	22 / 368 (5.98%)	13 / 364 (3.57%)	35 / 732 (4.78%)
occurrences (all)	31	13	44
Neutropenia			
subjects affected / exposed	89 / 368 (24.18%)	57 / 364 (15.66%)	146 / 732 (19.95%)
occurrences (all)	146	76	222
Thrombocytopenia			
subjects affected / exposed	55 / 368 (14.95%)	9 / 364 (2.47%)	64 / 732 (8.74%)
occurrences (all)	81	11	92
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	37 / 368 (10.05%)	28 / 364 (7.69%)	65 / 732 (8.88%)
occurrences (all)	45	33	78
Fatigue			
subjects affected / exposed	66 / 368 (17.93%)	55 / 364 (15.11%)	121 / 732 (16.53%)
occurrences (all)	81	76	157
Oedema peripheral			
subjects affected / exposed	69 / 368 (18.75%)	25 / 364 (6.87%)	94 / 732 (12.84%)
occurrences (all)	94	26	120
Pyrexia			

subjects affected / exposed	62 / 368 (16.85%)	32 / 364 (8.79%)	94 / 732 (12.84%)
occurrences (all)	73	38	111
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 368 (6.79%)	21 / 364 (5.77%)	46 / 732 (6.28%)
occurrences (all)	31	25	56
Aphthous ulcer			
subjects affected / exposed	21 / 368 (5.71%)	4 / 364 (1.10%)	25 / 732 (3.42%)
occurrences (all)	32	5	37
Constipation			
subjects affected / exposed	19 / 368 (5.16%)	25 / 364 (6.87%)	44 / 732 (6.01%)
occurrences (all)	24	34	58
Diarrhoea			
subjects affected / exposed	99 / 368 (26.90%)	49 / 364 (13.46%)	148 / 732 (20.22%)
occurrences (all)	143	66	209
Dry mouth			
subjects affected / exposed	23 / 368 (6.25%)	5 / 364 (1.37%)	28 / 732 (3.83%)
occurrences (all)	23	5	28
Mouth ulceration			
subjects affected / exposed	57 / 368 (15.49%)	13 / 364 (3.57%)	70 / 732 (9.56%)
occurrences (all)	104	24	128
Nausea			
subjects affected / exposed	51 / 368 (13.86%)	37 / 364 (10.16%)	88 / 732 (12.02%)
occurrences (all)	68	41	109
Stomatitis			
subjects affected / exposed	166 / 368 (45.11%)	28 / 364 (7.69%)	194 / 732 (26.50%)
occurrences (all)	263	32	295
Vomiting			
subjects affected / exposed	34 / 368 (9.24%)	30 / 364 (8.24%)	64 / 732 (8.74%)
occurrences (all)	44	35	79
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	65 / 368 (17.66%)	40 / 364 (10.99%)	105 / 732 (14.34%)
occurrences (all)	78	49	127
Dyspnoea			

subjects affected / exposed	32 / 368 (8.70%)	11 / 364 (3.02%)	43 / 732 (5.87%)
occurrences (all)	38	11	49
Epistaxis			
subjects affected / exposed	34 / 368 (9.24%)	2 / 364 (0.55%)	36 / 732 (4.92%)
occurrences (all)	37	2	39
Pneumonitis			
subjects affected / exposed	24 / 368 (6.52%)	1 / 364 (0.27%)	25 / 732 (3.42%)
occurrences (all)	24	1	25
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	36 / 368 (9.78%)	22 / 364 (6.04%)	58 / 732 (7.92%)
occurrences (all)	40	25	65
Rash			
subjects affected / exposed	70 / 368 (19.02%)	31 / 364 (8.52%)	101 / 732 (13.80%)
occurrences (all)	95	35	130
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 368 (6.79%)	16 / 364 (4.40%)	41 / 732 (5.60%)
occurrences (all)	31	18	49
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 368 (8.15%)	31 / 364 (8.52%)	61 / 732 (8.33%)
occurrences (all)	41	35	76
Back pain			
subjects affected / exposed	22 / 368 (5.98%)	33 / 364 (9.07%)	55 / 732 (7.51%)
occurrences (all)	26	34	60
Pain in extremity			
subjects affected / exposed	25 / 368 (6.79%)	28 / 364 (7.69%)	53 / 732 (7.24%)
occurrences (all)	26	32	58
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	42 / 368 (11.41%)	32 / 364 (8.79%)	74 / 732 (10.11%)
occurrences (all)	51	40	91
Pneumonia			
subjects affected / exposed	23 / 368 (6.25%)	3 / 364 (0.82%)	26 / 732 (3.55%)
occurrences (all)	23	3	26

Sinusitis			
subjects affected / exposed	21 / 368 (5.71%)	11 / 364 (3.02%)	32 / 732 (4.37%)
occurrences (all)	23	13	36
Upper respiratory tract infection			
subjects affected / exposed	42 / 368 (11.41%)	27 / 364 (7.42%)	69 / 732 (9.43%)
occurrences (all)	56	32	88
Urinary tract infection			
subjects affected / exposed	20 / 368 (5.43%)	18 / 364 (4.95%)	38 / 732 (5.19%)
occurrences (all)	25	29	54
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 368 (11.68%)	19 / 364 (5.22%)	62 / 732 (8.47%)
occurrences (all)	48	20	68
Hypercholesterolaemia			
subjects affected / exposed	42 / 368 (11.41%)	13 / 364 (3.57%)	55 / 732 (7.51%)
occurrences (all)	45	13	58
Hyperglycaemia			
subjects affected / exposed	40 / 368 (10.87%)	26 / 364 (7.14%)	66 / 732 (9.02%)
occurrences (all)	50	33	83
Hypertriglyceridaemia			
subjects affected / exposed	32 / 368 (8.70%)	16 / 364 (4.40%)	48 / 732 (6.56%)
occurrences (all)	48	21	69

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2010	The changes in this amendment were based on feedback from Investigators and institutional review boards/ethics committees, everolimus project-level updates and guidelines and clarifications and changes on study procedures and inclusion/exclusion criteria: Changes to criteria included: Bone marrow biopsy result prior to study start must be negative, Evidence of current CNS involvement with lymphoma; Changes to study procedures included: Hepatitis testing, pregnancy testing, and CNS involvement with lymphoma screening, end of treatment visit ≤ 7 days after stopping study drug, definition of relapse disease, additional biomarker assessment, study drug dosing and interruption, and concomitant medications.
08 November 2010	Several inclusion and exclusion criteria had been revised based on the feedback received from Investigators related to standard of care. As a consequence, the study design, the randomization and the analysis of the primary endpoint were revised: the minimum number of prior R-CHOP treatment cycles was reduced from 6 (in original protocol) to 5 cycles; the enrollment of patients who had received prior R-EPOCH treatment was allowed. Additionally, the randomization scheme was modified to stratify patients according to the type of prior rituximab-chemotherapy they received (R-CHOP vs. R-EPOCH). Patients enrolled in the original protocol were assigned to R-CHOP stratum; the analysis of the primary endpoint (disease-free survival) was modified to now use a stratified log-rank test to account for the new randomization scheme instead of an unstratified log-rank test as planned in the original protocol. This amendment also contained changes to ensure consistency across the everolimus clinical development program.
15 December 2011	The reason for this amendment was slow enrollment rate. Enrollment in this study had not met the expected rate as per the original assumptions, despite implementing practical and feasible approaches to increase the enrollment rate. The feasibility of the study within reasonable timelines was questionable with the current sample size. Therefore, in order not to jeopardize the feasibility of conducting the study within reasonable timelines, the sample size was modified to ensure completion of the study in a timely manner. The power of the study was reduced from 90% to 80%. Therefore the required number of DFS events was reduced from 374 to 279, resulting in sample size reduction 915 to 687 patients.
15 February 2013	The reason for this amendment was to include revised definition of relapsed disease, update protocol based on Investigator Brochure Edition 11, include Novartis guidance on prevention of pregnancy in clinical trials, and clarify and make changes on study procedures.
02 September 2013	The reason for this amendment was to increase the sample size, provide additional information on the unblinding and communication of interim OS results, and to include some clarifications related to study procedures. As the study remained blinded at the time of this amendment, this amendment did not affect the integrity of the study.
10 September 2014	The reason for the protocol amendment was to modify the censoring rule in the primary endpoint analysis for patients starting a new anticancer therapy; modify the follow-up of tumor assessment for patients starting a new anticancer therapy; and modify the definition of imaging modality change. As the study remained blinded at the time of this amendment, this amendment did not affect the integrity of the study.

29 July 2015	Globally there was one site that did not receive Amendment 7 approval by Last Patient Last Visit on 15-Jun-2016 (approval received 24-Jun-2016). This amendment was done for the following reasons: to remove the second IA and to conduct the final DFS analysis using a pre-defined fixed cut-off date of 31-Dec-2015 and the number of actual DFS events observed by that date, considering the long median study follow-up of 50 months (and at least 24 months follow-up for all patients by end of December 2015). Since there were fewer DFS events for the final DFS analysis, the power for primary endpoint was also amended; to maintain the interim overall survival (OS) analysis at the final DFS analysis (i.e., one IA for OS was removed) and perform the final OS analysis using a pre-defined fixed cutoff date of 31-Dec-2018 (5 years after randomization of the last patient) and the number of actual OS events observed by that date. Based on the number and timing of deaths observed in this study as of 22-Jun-2015 on pooled (i.e., blinded) data, the current projections suggested that it was highly unlikely that the originally targeted 338 OS events will ever be reached. Since there would be fewer death events at final OS analysis, the power for OS was also amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported