Clinical trial results:
A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma

Summary

EudraCT number	2011-006088-23
Trial protocol	SE GB BE AT NO IE CZ ES NL HU FI IT PL DK
Global end of trial date	25 April 2019

Results information

Result version number	v1
This version publication date	09 May 2020
First version publication date	09 May 2020

Trial information

Trial identification

Sponsor protocol code	116513

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01597908
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CDRB436B2302

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to establish the superiority of dabrafenib and trametinib combination therapy over vemurafenib monotherapy with respect to Overall Survival (OS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma
Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

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	04 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	Russian Federation: 38
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Brazil: 8

Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 101
Country: Number of subjects enrolled	Germany: 81
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Israel: 26
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Korea, Republic of: 7
Worldwide total number of subjects	704
EEA total number of subjects	464

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)	538
From 65 to 84 years	162
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 207 centers in 28 countries worldwide (Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, South Korea, Netherlands, New Zealand, Norway, Poland, Russian Federation, Spain, Sweden,Switzerland, Taiwan, Ukraine, UK and USA).

Pre-assignment

Screening details:

694 subjects were planned and 704 subjects (352 each in combination therapy arm and vemurafenib monotherapy arm) were actually randomized and analyzed. Subjects were stratified by LDH level (> the ULN versus ≤ ULN) and BRAF mutation (V600E versus V600K).

Period 1

Period 1 title	Randomized Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabrafenib plus Trametinib

Arm description:

Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	GSK2118436
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib 150 mg twice daily orally

Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	GSK1120212
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trametinib 2 mg once daily orally

Arm title	Vemurafenib

Arm description:

Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Arm type	Active comparator
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib 960 mg twice daily orally

Number of subjects in period 1	Dabrafenib plus Trametinib	Vemurafenib
Started	352	352
Safety Set	350	349
Completed	1	0
Not completed	351	352
Adverse event, serious fatal	217	238
Physician decision	6	3
Consent withdrawn by subject	26	22
Crossover to Dabrafenib&Trametinib	-	34
Lost to follow-up	9	16
Decision by sponsor	93	39

Baseline characteristics

Reporting groups	
Reporting group title	Dabrafenib plus Trametinib
Reporting group description:	
Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Vemurafenib
Reporting group description:	
Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	

Reporting group values	Dabrafenib plus Trametinib	Vemurafenib	Total
Number of subjects	352	352	704
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	274	264	538
From 65-84 years	75	87	162
85 years and over	3	1	4
Age Continuous Units: Years			
arithmetic mean	54.1	54.3	
standard deviation	± 13.83	± 14.06	-
Gender categorical Units: Subjects			
Female	144	172	316
Male	208	180	388
Race/Ethnicity, Customized Units: Subjects			
Asian - East Asian Heritage	8	8	16
White - Arabic/North African Heritage	4	2	6
White - White/Caucasian/European Heritage	339	339	678
White - Mixed Race	1	0	1
Mixed Race	0	1	1
African American/African Heritage	0	1	1
American Indian or Alaskan Native	0	1	1

End points

End points reporting groups

Reporting group title	Dabrafenib plus Trametinib
Reporting group description:	
Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Vemurafenib
Reporting group description:	
Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) was defined as the interval of time between the date of randomization and the date of death due to any cause. For patients who did not die, OS was censored at the date of last contact.	
End point type	Primary
End point timeframe:	
From the date of randomization until date of death due to any cause (up to approximately 6 years)	

End point values	Dabrafenib plus Trametinib	Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	352		
Units: Months				
median (confidence interval 95%)	26.0 (22.1 to 33.8)	17.8 (15.6 to 20.7)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Dabrafenib plus Trametinib v Vemurafenib
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.83

Secondary: Progression-Free Survival (PFS), as assessed by the Investigator

End point title	Progression-Free Survival (PFS), as assessed by the Investigator

End point description:

Progression-free survival (PFS) was defined as the interval of time between the date of randomization and the first documented occurrence of disease progression or death due to any cause. PFS for investigator-assessed response was summarized per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, which is a set of published rules defining when cancer patients improve (respond), stay the same (stabilize), or worsen (progress) during treatment. Disease progression was defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 millimeters (mm) or the appearance of at least 1 new lesion, or the worsening of non-target lesions significant enough to require study treatment discontinuation.

End point type	Secondary

End point timeframe:

From randomization until the earliest date of disease progression (PD) or death due to any cause (up to approximately 6 years)

End point values	Dabrafenib plus Trametinib	Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	352		
Units: Months				
median (confidence interval 95%)	12.1 (9.7 to 14.7)	7.3 (6.0 to 8.1)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Dabrafenib plus Trametinib v Vemurafenib
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.73

Secondary: Overall Response Rate (ORR) during randomized phase, as assessed by the Investigator

End point title	Overall Response Rate (ORR) during randomized phase, as assessed by the Investigator

End point description:

Overall response was defined as the percentage of confirmed responders (complete response [CR] + partial response [PR] per RECIST, Version 1.1) as summarized by Investigator assessment. CR was defined as the disappearance of all evidence of target lesions. PR was defined as at least a 30% reduction from Baseline in the sum of the longest diameter (LD) of all target lesions. Data were reported as those participants with measureable disease at Baseline.

End point type	Secondary

End point timeframe:

From randomization until the first documented complete response or partial response (up to approximately 6 years)

End point values	Dabrafenib plus Trametinib	Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	350		
Units: Percentage of Participants				
number (confidence interval 95%)	68 (62.3 to 72.4)	53 (47.2 to 57.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR), as assessed by the Investigator

End point title	Duration of Response (DOR), as assessed by the Investigator

End point description:

Duration of Response (DOR) was defined as the time from the first documented evidence of a CR (disappearance of all evidence of target lesions) or a PR (at least a 30% reduction from Baseline in the sum of the longest diameter of all target lesions) until disease progression or death due to any cause. PD was defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of at least1 new lesion, or the worsening of non-target lesions significant enough to require study treatment discontinuation. Data were summarized per RECIST, Version 1.1.

End point type	Secondary

End point timeframe:

From the time of the first documented response (CR or PR) until disease progression (up to approximately 6 years)

End point values	Dabrafenib plus Trametinib	Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	185		
Units: Months				
median (confidence interval 95%)	13.8 (11.3 to 18.6)	8.5 (7.4 to 9.3)		

Statistical analyses

Statistical analysis title	Duration of Response (DOR)
Comparison groups	Dabrafenib plus Trametinib v Vemurafenib
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.81

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to approximately 6 years.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Dabrafenib plus Trametinib

Reporting group description:

Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Vemurafenib

Reporting group description:

Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Crossover Dabrafenib plus Trametinib

Reporting group description:

With Protocol Amendment 7, patients still receiving study treatment on the Vemurafenib monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.

Reporting group title	All Patients

Reporting group description:

All randomized patients who received at least one dose of study treatment.

Serious adverse events	Dabrafenib plus Trametinib	Vemurafenib	Crossover Dabrafenib plus Trametinib
Total subjects affected by serious adverse events			
subjects affected / exposed	172 / 350 (49.14%)	139 / 349 (39.83%)	15 / 34 (44.12%)
number of deaths (all causes)	216	238	11
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Astrocytoma			

subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	13 / 350 (3.71%)	5 / 349 (1.43%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	8 / 15	4 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of adrenal gland			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	2 / 350 (0.57%)	3 / 349 (0.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoma in situ			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoma in situ of skin			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			

subjects affected / exposed	3 / 350 (0.86%)	23 / 349 (6.59%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	3 / 3	34 / 35	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo maligna			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 350 (0.57%)	7 / 349 (2.01%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 3	10 / 12	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin papilloma			

subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	3 / 350 (0.86%)	27 / 349 (7.74%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	4 / 4	31 / 31	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 350 (0.86%)	30 / 349 (8.60%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 3	50 / 51	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	5 / 350 (1.43%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocele			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 350 (0.86%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			

subjects affected / exposed	14 / 350 (4.00%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	15 / 17	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	3 / 350 (0.86%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	55 / 350 (15.71%)	6 / 349 (1.72%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	72 / 80	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 350 (0.57%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea exertional			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 350 (0.00%)	3 / 349 (0.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	6 / 350 (1.71%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Confusional state			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 350 (1.71%)	9 / 349 (2.58%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	4 / 6	8 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 350 (0.86%)	5 / 349 (1.43%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 3	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 350 (0.57%)	6 / 349 (1.72%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 350 (0.86%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ejection fraction decreased			
subjects affected / exposed	31 / 350 (8.86%)	1 / 349 (0.29%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	35 / 37	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	4 / 350 (1.14%)	6 / 349 (1.72%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 4	6 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pelvic fracture			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation necrosis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 350 (0.86%)	4 / 349 (1.15%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 5	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	2 / 350 (0.57%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 350 (0.00%)	5 / 349 (1.43%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem haemorrhage			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	3 / 350 (0.86%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 350 (1.14%)	2 / 349 (0.57%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	1 / 4	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinopathy			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal degeneration			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			

subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous detachment			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 350 (0.86%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			

subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukoplakia oral			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 350 (1.43%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			

subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	8 / 350 (2.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	6 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	4 / 350 (1.14%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			

subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 350 (0.00%)	2 / 349 (0.57%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic cutaneous lupus erythematosus			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema nodosum			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purpura			

subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	3 / 350 (0.86%)	3 / 349 (0.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 3	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 350 (0.29%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	4 / 350 (1.14%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall haematoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	2 / 350 (0.57%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess soft tissue			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	5 / 350 (1.43%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal abscess			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	4 / 350 (1.14%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	3 / 350 (0.86%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 350 (0.00%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 350 (0.29%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			

subjects affected / exposed	4 / 350 (1.14%)	6 / 349 (1.72%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 4	1 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 350 (0.86%)	0 / 349 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			

subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 349 (0.29%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	10 / 350 (2.86%)	1 / 349 (0.29%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	2 / 11	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	8 / 350 (2.29%)	2 / 349 (0.57%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	10 / 11	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	5 / 350 (1.43%)	0 / 349 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	319 / 699 (45.64%)		
number of deaths (all causes)	465		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Astrocytoma			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	20 / 699 (2.86%)		
occurrences causally related to treatment / all	15 / 23		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of adrenal gland			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	5 / 699 (0.72%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Carcinoma in situ			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Carcinoma in situ of skin			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colon adenoma			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Keratoacanthoma			
subjects affected / exposed	26 / 699 (3.72%)		
occurrences causally related to treatment / all	37 / 39		
deaths causally related to treatment / all	0 / 0		
Lentigo maligna			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	3 / 699 (0.43%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lymphoma			

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	9 / 699 (1.29%)			
occurrences causally related to treatment / all	10 / 15			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm malignant				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatic adenoma				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal adenocarcinoma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin papilloma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	30 / 699 (4.29%)			
occurrences causally related to treatment / all	35 / 35			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	33 / 699 (4.72%)			
occurrences causally related to treatment / all	52 / 54			
deaths causally related to treatment / all	0 / 0			
Superficial spreading melanoma stage unspecified				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	5 / 699 (0.72%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Lymphocele				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicose vein				

subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 699 (0.43%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	14 / 699 (2.00%)		
occurrences causally related to treatment / all	15 / 17		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	4 / 699 (0.57%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	3 / 699 (0.43%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Malaise			

subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	61 / 699 (8.73%)		
occurrences causally related to treatment / all	77 / 86		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine haemorrhage			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	4 / 699 (0.57%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				

subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	3 / 699 (0.43%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	7 / 699 (1.00%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 699 (2.15%)		
occurrences causally related to treatment / all	12 / 15		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 699 (1.14%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		

Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	8 / 699 (1.14%)			
occurrences causally related to treatment / all	6 / 8			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase increased				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	34 / 699 (4.86%)			
occurrences causally related to treatment / all	37 / 41			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	10 / 699 (1.43%)			
occurrences causally related to treatment / all	9 / 11			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin I increased				

subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	2 / 699 (0.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural complication			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation necrosis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	2 / 699 (0.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular pseudoaneurysm				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound dehiscence				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Acute myocardial infarction				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	7 / 699 (1.00%)			
occurrences causally related to treatment / all	5 / 9			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	4 / 699 (0.57%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Pericardial effusion				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	5 / 699 (0.72%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachyarrhythmia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain stem haemorrhage				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral haemorrhage				
subjects affected / exposed	4 / 699 (0.57%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 3			
Cerebral ischaemia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebrovascular accident				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Haemorrhagic stroke				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Headache				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				

subjects affected / exposed	7 / 699 (1.00%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cataract				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chorioretinopathy				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Eye haemorrhage				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Glaucoma				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal degeneration				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal tear				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal vein occlusion				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Uveitis				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vision blurred				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous detachment				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				

subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal perforation				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal pain				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal pseudo-obstruction				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukoplakia oral				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	6 / 699 (0.86%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal polyp				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	9 / 699 (1.29%)			
occurrences causally related to treatment / all	6 / 9			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct obstruction				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	6 / 699 (0.86%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gallbladder polyp				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertransaminasaemia				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Actinic keratosis				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Chronic cutaneous lupus erythematosus				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis bullous				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema nodosum				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Purpura				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	6 / 699 (0.86%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	0 / 0			
Rash erythematous				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Skin lesion				

subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 699 (0.43%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Calculus urinary			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephropathy toxic			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Prerenal failure			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	4 / 699 (0.57%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Urethral stenosis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	2 / 699 (0.29%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Chest wall haematoma			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	2 / 699 (0.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			

subjects affected / exposed	2 / 699 (0.29%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess soft tissue			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	6 / 699 (0.86%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corneal abscess				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	4 / 699 (0.57%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				

subjects affected / exposed	5 / 699 (0.72%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Haematoma infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Helicobacter infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	3 / 699 (0.43%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 699 (0.29%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal candidiasis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	10 / 699 (1.43%)			
occurrences causally related to treatment / all	1 / 11			
deaths causally related to treatment / all	0 / 1			
Post procedural infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 699 (0.57%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	12 / 699 (1.72%)			
occurrences causally related to treatment / all	2 / 13			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 699 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	10 / 699 (1.43%)		
occurrences causally related to treatment / all	11 / 13		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 699 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	5 / 699 (0.72%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dabrafenib plus Trametinib	Vemurafenib	Crossover Dabrafenib plus Trametinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	338 / 350 (96.57%)	341 / 349 (97.71%)	32 / 34 (94.12%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 350 (0.57%)	21 / 349 (6.02%)	0 / 34 (0.00%)
occurrences (all)	2	23	0
Skin papilloma			
subjects affected / exposed	9 / 350 (2.57%)	85 / 349 (24.36%)	1 / 34 (2.94%)
occurrences (all)	13	116	3
Vascular disorders			

Hypertension			
subjects affected / exposed	109 / 350 (31.14%)	83 / 349 (23.78%)	4 / 34 (11.76%)
occurrences (all)	173	114	4
Lymphoedema			
subjects affected / exposed	25 / 350 (7.14%)	6 / 349 (1.72%)	2 / 34 (5.88%)
occurrences (all)	27	6	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	65 / 350 (18.57%)	62 / 349 (17.77%)	8 / 34 (23.53%)
occurrences (all)	95	89	11
Chills			
subjects affected / exposed	113 / 350 (32.29%)	28 / 349 (8.02%)	6 / 34 (17.65%)
occurrences (all)	265	32	11
Fatigue			
subjects affected / exposed	116 / 350 (33.14%)	116 / 349 (33.24%)	1 / 34 (2.94%)
occurrences (all)	161	126	2
Hypothermia			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	2 / 34 (5.88%)
occurrences (all)	3	1	2
Influenza like illness			
subjects affected / exposed	36 / 350 (10.29%)	13 / 349 (3.72%)	2 / 34 (5.88%)
occurrences (all)	50	14	4
Malaise			
subjects affected / exposed	16 / 350 (4.57%)	8 / 349 (2.29%)	2 / 34 (5.88%)
occurrences (all)	22	8	2
Oedema peripheral			
subjects affected / exposed	61 / 350 (17.43%)	45 / 349 (12.89%)	3 / 34 (8.82%)
occurrences (all)	81	60	3
Pain			
subjects affected / exposed	18 / 350 (5.14%)	15 / 349 (4.30%)	2 / 34 (5.88%)
occurrences (all)	38	15	2
Peripheral swelling			
subjects affected / exposed	25 / 350 (7.14%)	12 / 349 (3.44%)	3 / 34 (8.82%)
occurrences (all)	45	14	3
Pyrexia			

subjects affected / exposed	184 / 350 (52.57%)	72 / 349 (20.63%)	16 / 34 (47.06%)
occurrences (all)	587	106	61
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	88 / 350 (25.14%)	40 / 349 (11.46%)	6 / 34 (17.65%)
occurrences (all)	114	46	10
Dyspnoea			
subjects affected / exposed	34 / 350 (9.71%)	29 / 349 (8.31%)	1 / 34 (2.94%)
occurrences (all)	41	31	1
Epistaxis			
subjects affected / exposed	32 / 350 (9.14%)	6 / 349 (1.72%)	4 / 34 (11.76%)
occurrences (all)	52	7	5
Nasal dryness			
subjects affected / exposed	3 / 350 (0.86%)	2 / 349 (0.57%)	2 / 34 (5.88%)
occurrences (all)	3	2	2
Oropharyngeal pain			
subjects affected / exposed	27 / 350 (7.71%)	19 / 349 (5.44%)	1 / 34 (2.94%)
occurrences (all)	32	23	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 350 (6.29%)	33 / 349 (9.46%)	0 / 34 (0.00%)
occurrences (all)	24	36	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	54 / 350 (15.43%)	54 / 349 (15.47%)	2 / 34 (5.88%)
occurrences (all)	63	60	4
Aspartate aminotransferase increased			
subjects affected / exposed	47 / 350 (13.43%)	42 / 349 (12.03%)	3 / 34 (8.82%)
occurrences (all)	61	44	5
Blood alkaline phosphatase increased			
subjects affected / exposed	30 / 350 (8.57%)	29 / 349 (8.31%)	0 / 34 (0.00%)
occurrences (all)	38	33	0
Blood creatine phosphokinase increased			
subjects affected / exposed	12 / 350 (3.43%)	4 / 349 (1.15%)	5 / 34 (14.71%)
occurrences (all)	21	5	5

Blood creatinine increased			
subjects affected / exposed	16 / 350 (4.57%)	36 / 349 (10.32%)	2 / 34 (5.88%)
occurrences (all)	19	46	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	23 / 350 (6.57%)	9 / 349 (2.58%)	1 / 34 (2.94%)
occurrences (all)	29	10	1
C-reactive protein increased			
subjects affected / exposed	12 / 350 (3.43%)	1 / 349 (0.29%)	2 / 34 (5.88%)
occurrences (all)	13	1	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	45 / 350 (12.86%)	35 / 349 (10.03%)	1 / 34 (2.94%)
occurrences (all)	59	39	1
Neutrophil count decreased			
subjects affected / exposed	15 / 350 (4.29%)	1 / 349 (0.29%)	2 / 34 (5.88%)
occurrences (all)	31	1	2
Weight decreased			
subjects affected / exposed	21 / 350 (6.00%)	42 / 349 (12.03%)	1 / 34 (2.94%)
occurrences (all)	22	45	1
White blood cell count decreased			
subjects affected / exposed	13 / 350 (3.71%)	3 / 349 (0.86%)	2 / 34 (5.88%)
occurrences (all)	20	3	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 350 (1.71%)	5 / 349 (1.43%)	2 / 34 (5.88%)
occurrences (all)	8	5	3
Sunburn			
subjects affected / exposed	5 / 350 (1.43%)	47 / 349 (13.47%)	0 / 34 (0.00%)
occurrences (all)	5	68	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	4 / 350 (1.14%)	1 / 349 (0.29%)	2 / 34 (5.88%)
occurrences (all)	4	1	2
Dizziness			
subjects affected / exposed	46 / 350 (13.14%)	24 / 349 (6.88%)	3 / 34 (8.82%)
occurrences (all)	71	28	4

Dysgeusia			
subjects affected / exposed	23 / 350 (6.57%)	48 / 349 (13.75%)	2 / 34 (5.88%)
occurrences (all)	26	54	2
Headache			
subjects affected / exposed	123 / 350 (35.14%)	86 / 349 (24.64%)	8 / 34 (23.53%)
occurrences (all)	221	114	10
Hypoaesthesia			
subjects affected / exposed	9 / 350 (2.57%)	11 / 349 (3.15%)	2 / 34 (5.88%)
occurrences (all)	11	11	2
Paraesthesia			
subjects affected / exposed	17 / 350 (4.86%)	18 / 349 (5.16%)	0 / 34 (0.00%)
occurrences (all)	22	20	0
Syncope			
subjects affected / exposed	13 / 350 (3.71%)	4 / 349 (1.15%)	3 / 34 (8.82%)
occurrences (all)	16	4	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 350 (8.29%)	20 / 349 (5.73%)	3 / 34 (8.82%)
occurrences (all)	35	21	4
Leukopenia			
subjects affected / exposed	17 / 350 (4.86%)	7 / 349 (2.01%)	6 / 34 (17.65%)
occurrences (all)	24	14	18
Lymphopenia			
subjects affected / exposed	9 / 350 (2.57%)	9 / 349 (2.58%)	2 / 34 (5.88%)
occurrences (all)	17	9	3
Neutropenia			
subjects affected / exposed	37 / 350 (10.57%)	6 / 349 (1.72%)	9 / 34 (26.47%)
occurrences (all)	57	10	28
Thrombocytopenia			
subjects affected / exposed	11 / 350 (3.14%)	2 / 349 (0.57%)	3 / 34 (8.82%)
occurrences (all)	12	2	6
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	5 / 350 (1.43%)	3 / 349 (0.86%)	2 / 34 (5.88%)
occurrences (all)	5	3	2
Eye disorders			

Vision blurred			
subjects affected / exposed	23 / 350 (6.57%)	18 / 349 (5.16%)	1 / 34 (2.94%)
occurrences (all)	25	19	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	41 / 350 (11.71%)	33 / 349 (9.46%)	3 / 34 (8.82%)
occurrences (all)	52	35	4
Abdominal pain upper			
subjects affected / exposed	38 / 350 (10.86%)	36 / 349 (10.32%)	4 / 34 (11.76%)
occurrences (all)	61	45	4
Constipation			
subjects affected / exposed	58 / 350 (16.57%)	25 / 349 (7.16%)	7 / 34 (20.59%)
occurrences (all)	65	25	11
Diarrhoea			
subjects affected / exposed	131 / 350 (37.43%)	137 / 349 (39.26%)	5 / 34 (14.71%)
occurrences (all)	233	234	6
Dry mouth			
subjects affected / exposed	27 / 350 (7.71%)	8 / 349 (2.29%)	1 / 34 (2.94%)
occurrences (all)	30	8	1
Dyspepsia			
subjects affected / exposed	20 / 350 (5.71%)	15 / 349 (4.30%)	3 / 34 (8.82%)
occurrences (all)	22	23	5
Haemorrhoids			
subjects affected / exposed	4 / 350 (1.14%)	7 / 349 (2.01%)	3 / 34 (8.82%)
occurrences (all)	5	9	3
Nausea			
subjects affected / exposed	125 / 350 (35.71%)	131 / 349 (37.54%)	8 / 34 (23.53%)
occurrences (all)	204	162	8
Vomiting			
subjects affected / exposed	111 / 350 (31.71%)	57 / 349 (16.33%)	4 / 34 (11.76%)
occurrences (all)	196	85	5
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	10 / 350 (2.86%)	24 / 349 (6.88%)	2 / 34 (5.88%)
occurrences (all)	22	29	4
Alopecia			

subjects affected / exposed	26 / 350 (7.43%)	138 / 349 (39.54%)	0 / 34 (0.00%)
occurrences (all)	27	147	0
Dermatitis acneiform			
subjects affected / exposed	25 / 350 (7.14%)	20 / 349 (5.73%)	1 / 34 (2.94%)
occurrences (all)	30	21	2
Dry skin			
subjects affected / exposed	34 / 350 (9.71%)	70 / 349 (20.06%)	5 / 34 (14.71%)
occurrences (all)	40	79	5
Eczema			
subjects affected / exposed	28 / 350 (8.00%)	13 / 349 (3.72%)	4 / 34 (11.76%)
occurrences (all)	34	13	6
Erythema			
subjects affected / exposed	41 / 350 (11.71%)	44 / 349 (12.61%)	2 / 34 (5.88%)
occurrences (all)	50	57	3
Hyperhidrosis			
subjects affected / exposed	18 / 350 (5.14%)	4 / 349 (1.15%)	3 / 34 (8.82%)
occurrences (all)	29	4	6
Hyperkeratosis			
subjects affected / exposed	26 / 350 (7.43%)	103 / 349 (29.51%)	0 / 34 (0.00%)
occurrences (all)	33	135	0
Keratosis pilaris			
subjects affected / exposed	5 / 350 (1.43%)	44 / 349 (12.61%)	1 / 34 (2.94%)
occurrences (all)	7	49	1
Night sweats			
subjects affected / exposed	24 / 350 (6.86%)	8 / 349 (2.29%)	2 / 34 (5.88%)
occurrences (all)	34	12	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	10 / 350 (2.86%)	54 / 349 (15.47%)	1 / 34 (2.94%)
occurrences (all)	13	59	1
Palmoplantar keratoderma			
subjects affected / exposed	9 / 350 (2.57%)	21 / 349 (6.02%)	1 / 34 (2.94%)
occurrences (all)	9	21	1
Photosensitivity reaction			
subjects affected / exposed	17 / 350 (4.86%)	88 / 349 (25.21%)	0 / 34 (0.00%)
occurrences (all)	18	110	0

Pruritus			
subjects affected / exposed	40 / 350 (11.43%)	80 / 349 (22.92%)	0 / 34 (0.00%)
occurrences (all)	47	94	0
Rash			
subjects affected / exposed	95 / 350 (27.14%)	153 / 349 (43.84%)	4 / 34 (11.76%)
occurrences (all)	168	190	4
Rash maculo-papular			
subjects affected / exposed	12 / 350 (3.43%)	27 / 349 (7.74%)	1 / 34 (2.94%)
occurrences (all)	14	30	1
Skin exfoliation			
subjects affected / exposed	6 / 350 (1.71%)	11 / 349 (3.15%)	2 / 34 (5.88%)
occurrences (all)	6	11	3
Skin lesion			
subjects affected / exposed	13 / 350 (3.71%)	9 / 349 (2.58%)	2 / 34 (5.88%)
occurrences (all)	17	10	2
Skin mass			
subjects affected / exposed	5 / 350 (1.43%)	4 / 349 (1.15%)	2 / 34 (5.88%)
occurrences (all)	5	4	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	104 / 350 (29.71%)	182 / 349 (52.15%)	9 / 34 (26.47%)
occurrences (all)	179	299	11
Back pain			
subjects affected / exposed	43 / 350 (12.29%)	29 / 349 (8.31%)	5 / 34 (14.71%)
occurrences (all)	60	31	5
Muscle spasms			
subjects affected / exposed	47 / 350 (13.43%)	13 / 349 (3.72%)	4 / 34 (11.76%)
occurrences (all)	67	14	5
Musculoskeletal chest pain			
subjects affected / exposed	19 / 350 (5.43%)	10 / 349 (2.87%)	0 / 34 (0.00%)
occurrences (all)	19	11	0
Musculoskeletal pain			
subjects affected / exposed	24 / 350 (6.86%)	27 / 349 (7.74%)	4 / 34 (11.76%)
occurrences (all)	27	27	4
Myalgia			

subjects affected / exposed	76 / 350 (21.71%)	56 / 349 (16.05%)	8 / 34 (23.53%)
occurrences (all)	113	68	9
Pain in extremity			
subjects affected / exposed	50 / 350 (14.29%)	42 / 349 (12.03%)	2 / 34 (5.88%)
occurrences (all)	76	60	2
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	3 / 350 (0.86%)	0 / 349 (0.00%)	2 / 34 (5.88%)
occurrences (all)	3	0	2
Conjunctivitis			
subjects affected / exposed	14 / 350 (4.00%)	37 / 349 (10.60%)	1 / 34 (2.94%)
occurrences (all)	16	46	1
Folliculitis			
subjects affected / exposed	18 / 350 (5.14%)	25 / 349 (7.16%)	1 / 34 (2.94%)
occurrences (all)	28	27	2
Influenza			
subjects affected / exposed	31 / 350 (8.86%)	9 / 349 (2.58%)	2 / 34 (5.88%)
occurrences (all)	47	11	3
Nasopharyngitis			
subjects affected / exposed	64 / 350 (18.29%)	32 / 349 (9.17%)	6 / 34 (17.65%)
occurrences (all)	128	49	8
Onychomycosis			
subjects affected / exposed	4 / 350 (1.14%)	1 / 349 (0.29%)	2 / 34 (5.88%)
occurrences (all)	4	1	2
Pharyngitis			
subjects affected / exposed	19 / 350 (5.43%)	7 / 349 (2.01%)	1 / 34 (2.94%)
occurrences (all)	21	7	1
Pneumonia			
subjects affected / exposed	4 / 350 (1.14%)	1 / 349 (0.29%)	4 / 34 (11.76%)
occurrences (all)	4	1	5
Rhinitis			
subjects affected / exposed	14 / 350 (4.00%)	8 / 349 (2.29%)	2 / 34 (5.88%)
occurrences (all)	15	9	2
Upper respiratory tract infection			
subjects affected / exposed	23 / 350 (6.57%)	14 / 349 (4.01%)	3 / 34 (8.82%)
occurrences (all)	36	22	3

Urinary tract infection			
subjects affected / exposed	31 / 350 (8.86%)	7 / 349 (2.01%)	3 / 34 (8.82%)
occurrences (all)	53	8	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	47 / 350 (13.43%)	72 / 349 (20.63%)	6 / 34 (17.65%)
occurrences (all)	62	86	7
Hyperglycaemia			
subjects affected / exposed	20 / 350 (5.71%)	12 / 349 (3.44%)	3 / 34 (8.82%)
occurrences (all)	27	14	3
Increased appetite			
subjects affected / exposed	2 / 350 (0.57%)	1 / 349 (0.29%)	3 / 34 (8.82%)
occurrences (all)	2	1	3

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	679 / 699 (97.14%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	23 / 699 (3.29%)		
occurrences (all)	25		
Skin papilloma			
subjects affected / exposed	95 / 699 (13.59%)		
occurrences (all)	132		
Vascular disorders			
Hypertension			
subjects affected / exposed	195 / 699 (27.90%)		
occurrences (all)	291		
Lymphoedema			
subjects affected / exposed	33 / 699 (4.72%)		
occurrences (all)	36		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	131 / 699 (18.74%)		
occurrences (all)	195		
Chills			

subjects affected / exposed	147 / 699 (21.03%)		
occurrences (all)	308		
Fatigue			
subjects affected / exposed	232 / 699 (33.19%)		
occurrences (all)	289		
Hypothermia			
subjects affected / exposed	4 / 699 (0.57%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	51 / 699 (7.30%)		
occurrences (all)	68		
Malaise			
subjects affected / exposed	24 / 699 (3.43%)		
occurrences (all)	32		
Oedema peripheral			
subjects affected / exposed	108 / 699 (15.45%)		
occurrences (all)	144		
Pain			
subjects affected / exposed	35 / 699 (5.01%)		
occurrences (all)	55		
Peripheral swelling			
subjects affected / exposed	40 / 699 (5.72%)		
occurrences (all)	62		
Pyrexia			
subjects affected / exposed	267 / 699 (38.20%)		
occurrences (all)	754		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	132 / 699 (18.88%)		
occurrences (all)	170		
Dyspnoea			
subjects affected / exposed	64 / 699 (9.16%)		
occurrences (all)	73		
Epistaxis			

subjects affected / exposed	41 / 699 (5.87%)		
occurrences (all)	64		
Nasal dryness			
subjects affected / exposed	7 / 699 (1.00%)		
occurrences (all)	7		
Oropharyngeal pain			
subjects affected / exposed	47 / 699 (6.72%)		
occurrences (all)	56		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	55 / 699 (7.87%)		
occurrences (all)	60		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	110 / 699 (15.74%)		
occurrences (all)	127		
Aspartate aminotransferase increased			
subjects affected / exposed	92 / 699 (13.16%)		
occurrences (all)	110		
Blood alkaline phosphatase increased			
subjects affected / exposed	59 / 699 (8.44%)		
occurrences (all)	71		
Blood creatine phosphokinase increased			
subjects affected / exposed	20 / 699 (2.86%)		
occurrences (all)	31		
Blood creatinine increased			
subjects affected / exposed	53 / 699 (7.58%)		
occurrences (all)	67		
Blood lactate dehydrogenase increased			
subjects affected / exposed	33 / 699 (4.72%)		
occurrences (all)	40		
C-reactive protein increased			
subjects affected / exposed	15 / 699 (2.15%)		
occurrences (all)	16		
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	81 / 699 (11.59%)		
occurrences (all)	99		
Neutrophil count decreased			
subjects affected / exposed	18 / 699 (2.58%)		
occurrences (all)	34		
Weight decreased			
subjects affected / exposed	64 / 699 (9.16%)		
occurrences (all)	68		
White blood cell count decreased			
subjects affected / exposed	18 / 699 (2.58%)		
occurrences (all)	25		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 699 (1.72%)		
occurrences (all)	16		
Sunburn			
subjects affected / exposed	52 / 699 (7.44%)		
occurrences (all)	73		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	7 / 699 (1.00%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	73 / 699 (10.44%)		
occurrences (all)	103		
Dysgeusia			
subjects affected / exposed	73 / 699 (10.44%)		
occurrences (all)	82		
Headache			
subjects affected / exposed	214 / 699 (30.62%)		
occurrences (all)	345		
Hypoaesthesia			
subjects affected / exposed	21 / 699 (3.00%)		
occurrences (all)	24		
Paraesthesia			

subjects affected / exposed	35 / 699 (5.01%)		
occurrences (all)	42		
Syncope			
subjects affected / exposed	19 / 699 (2.72%)		
occurrences (all)	24		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	52 / 699 (7.44%)		
occurrences (all)	60		
Leukopenia			
subjects affected / exposed	29 / 699 (4.15%)		
occurrences (all)	56		
Lymphopenia			
subjects affected / exposed	20 / 699 (2.86%)		
occurrences (all)	29		
Neutropenia			
subjects affected / exposed	51 / 699 (7.30%)		
occurrences (all)	95		
Thrombocytopenia			
subjects affected / exposed	16 / 699 (2.29%)		
occurrences (all)	20		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	10 / 699 (1.43%)		
occurrences (all)	10		
Eye disorders			
Vision blurred			
subjects affected / exposed	42 / 699 (6.01%)		
occurrences (all)	45		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	75 / 699 (10.73%)		
occurrences (all)	91		
Abdominal pain upper			
subjects affected / exposed	78 / 699 (11.16%)		
occurrences (all)	110		
Constipation			

subjects affected / exposed	89 / 699 (12.73%)		
occurrences (all)	101		
Diarrhoea			
subjects affected / exposed	268 / 699 (38.34%)		
occurrences (all)	473		
Dry mouth			
subjects affected / exposed	36 / 699 (5.15%)		
occurrences (all)	39		
Dyspepsia			
subjects affected / exposed	37 / 699 (5.29%)		
occurrences (all)	50		
Haemorrhoids			
subjects affected / exposed	14 / 699 (2.00%)		
occurrences (all)	17		
Nausea			
subjects affected / exposed	261 / 699 (37.34%)		
occurrences (all)	374		
Vomiting			
subjects affected / exposed	172 / 699 (24.61%)		
occurrences (all)	286		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	36 / 699 (5.15%)		
occurrences (all)	55		
Alopecia			
subjects affected / exposed	164 / 699 (23.46%)		
occurrences (all)	174		
Dermatitis acneiform			
subjects affected / exposed	46 / 699 (6.58%)		
occurrences (all)	53		
Dry skin			
subjects affected / exposed	106 / 699 (15.16%)		
occurrences (all)	124		
Eczema			
subjects affected / exposed	45 / 699 (6.44%)		
occurrences (all)	53		

Erythema				
subjects affected / exposed	86 / 699 (12.30%)			
occurrences (all)	110			
Hyperhidrosis				
subjects affected / exposed	25 / 699 (3.58%)			
occurrences (all)	39			
Hyperkeratosis				
subjects affected / exposed	129 / 699 (18.45%)			
occurrences (all)	168			
Keratosis pilaris				
subjects affected / exposed	50 / 699 (7.15%)			
occurrences (all)	57			
Night sweats				
subjects affected / exposed	33 / 699 (4.72%)			
occurrences (all)	49			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	64 / 699 (9.16%)			
occurrences (all)	73			
Palmoplantar keratoderma				
subjects affected / exposed	31 / 699 (4.43%)			
occurrences (all)	31			
Photosensitivity reaction				
subjects affected / exposed	105 / 699 (15.02%)			
occurrences (all)	128			
Pruritus				
subjects affected / exposed	120 / 699 (17.17%)			
occurrences (all)	141			
Rash				
subjects affected / exposed	248 / 699 (35.48%)			
occurrences (all)	362			
Rash maculo-papular				
subjects affected / exposed	39 / 699 (5.58%)			
occurrences (all)	45			
Skin exfoliation				

subjects affected / exposed	19 / 699 (2.72%)		
occurrences (all)	20		
Skin lesion			
subjects affected / exposed	23 / 699 (3.29%)		
occurrences (all)	29		
Skin mass			
subjects affected / exposed	11 / 699 (1.57%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	288 / 699 (41.20%)		
occurrences (all)	489		
Back pain			
subjects affected / exposed	77 / 699 (11.02%)		
occurrences (all)	96		
Muscle spasms			
subjects affected / exposed	63 / 699 (9.01%)		
occurrences (all)	86		
Musculoskeletal chest pain			
subjects affected / exposed	29 / 699 (4.15%)		
occurrences (all)	30		
Musculoskeletal pain			
subjects affected / exposed	54 / 699 (7.73%)		
occurrences (all)	58		
Myalgia			
subjects affected / exposed	134 / 699 (19.17%)		
occurrences (all)	190		
Pain in extremity			
subjects affected / exposed	94 / 699 (13.45%)		
occurrences (all)	138		
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	5 / 699 (0.72%)		
occurrences (all)	5		
Conjunctivitis			

subjects affected / exposed	52 / 699 (7.44%)		
occurrences (all)	63		
Folliculitis			
subjects affected / exposed	43 / 699 (6.15%)		
occurrences (all)	57		
Influenza			
subjects affected / exposed	41 / 699 (5.87%)		
occurrences (all)	61		
Nasopharyngitis			
subjects affected / exposed	100 / 699 (14.31%)		
occurrences (all)	185		
Onychomycosis			
subjects affected / exposed	7 / 699 (1.00%)		
occurrences (all)	7		
Pharyngitis			
subjects affected / exposed	27 / 699 (3.86%)		
occurrences (all)	29		
Pneumonia			
subjects affected / exposed	9 / 699 (1.29%)		
occurrences (all)	10		
Rhinitis			
subjects affected / exposed	24 / 699 (3.43%)		
occurrences (all)	26		
Upper respiratory tract infection			
subjects affected / exposed	40 / 699 (5.72%)		
occurrences (all)	61		
Urinary tract infection			
subjects affected / exposed	41 / 699 (5.87%)		
occurrences (all)	65		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	123 / 699 (17.60%)		
occurrences (all)	155		
Hyperglycaemia			
subjects affected / exposed	35 / 699 (5.01%)		
occurrences (all)	44		

Increased appetite subjects affected / exposed occurrences (all)	6 / 699 (0.86%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2012	Amendment 1 made the following changes based on feedback from the FDA: 1) Included new requirements for subjects that remain on study treatment after radiographic disease progression; 2) Required that study treatment will be interrupted for any treatment-related AE of grade 3; 3) Required that rash of >= grade 3 must resolve to =<grade 1 before study treatment can be re-started; 4) Removed the allowance for palliative radiation therapy and stated that subjects should not receive palliative radiation therapy prior to documented disease progression; 5) Added an ophthalmic examination at week 4 to enhance the monitoring and more accurately assess the incidence of ophthalmic toxicities; 6) Clarified that the LDH value collected within 14 days of randomization will be used for stratification; 7) Added bicarbonate and chloride to the clinical chemistry parameters; 8) Requirements for cervical and rectal exams, at baseline and end of study. Clarifications of inclusion criteria no. 5, exclusion criteria no. 8 and exclusion criteria no. 10 were made; and exclusion criteria no. 12 added. Changes were made to the vemurafenib label: 1) Addition of QT interval guidance for vemurafenib; 2) Addition of magnesium to clinical chemistry to ensure adequate electrolyte monitoring; 3) Addition of ECG at day 15; 4) Addition of chemistry panel at day 15 to monitor electrolytes; 5) Extension of use of contraception to 6 months in men and women posttreatment. The following additional changes were made to the study protocol: 1) Clarified the definition of asymptomatic hypertension as well as withholding and stopping criteria for QTc-prolongation; 2) Addition of basal cell carcinoma and secondary melanoma to protocol-specific SAEs for new malignancies; 3) Updated prohibited medications and medications to be used with caution based on new data; 5) Correction of typographical errors and change to UK English.
29 June 2012	Country-specific Amendment 02 made the following changes to the study protocol: 1) Added the valvular toxicity withholding criteria for subjects enrolled in France, as requested by the French regulatory agency; 2) Added potassium level monitoring within 72 hours prior to first dose for subjects enrolled in France, as per feedback from French regulatory agency.
22 October 2013	Amendment 03: 1) Revised inclusion criterion #4 and inclusion criterion #7; 2) Added new Section 4.2.2 outlining process for subjects who continue study treatment after disease progression; 3) Removed language prohibiting the intake of food and drink containing grapefruit, Seville oranges, and pommelos; 4) Revised Table 7 regarding dose modifications for LVEF decrease; 5) Clarified in Table 10 Guidelines for Supportive Care of Rash that topical steroids or antibiotics should be used for prevention/prophylaxis; 6) Revised Section 5.8.5.3 to include monitoring guidelines for new cutaneous and non-cutaneous malignancies; 7) Added text in Section 5.8.6.1 Guidelines for pyrexia regarding monitoring of serum creatinine and other evidence of renal function for severe cases of pyrexia; 8) Clarified in Table 16 Management and Dose Modification Guidelines for visual changes that central serous retinopathy and retinal vein occulusion are reportable SAEs, and trametinib should be interrupted or reduced for visual changes. In addition, guidance on action to be taken for cases of uveitis; 9) Revised prohibited and cautionary medications text and tables based on emerging data; 10) Revised text to clarify that the removal or reduction of lesions that are being followed for disease assessments is considered anti-cancer therapy and prohibited during the study; 11) Revised Section 7.3.2.5 to include reporting requirements and actions that should be taken for new primary cancers and treatment emergent malignancies; 12) Revised text in Section 7.3.3.1 to include new guidance for female and male effective contraceptive methods after last dose of study treatment; 13) Added a note within the footnotes of Table 23 Laboratory assessments to include laboratory tests that should be collected to confirm diagnosis of pancreatitis; 14) Added new Section 12.10 Appendix 10 to include new monitoring guidelines for malignancies for subjects enrolled in France (country-specific amendment).

26 February 2014	Amendment 04 made the following major changes to the study protocol all other changes were for clarification or administrative purposes: 1) Revised study design language regarding when study will be considered closed and also, removed reference to the rollover study as an option for subjects; 2) Added information regarding the approval of dabrafenib and trametinib in various countries; 3) Added new data for the integrated safety population for dabrafenib; 4) Revised effective contraception requirements for women to align with the correct timing, per vemurafenib label; 5) Revised dose modification guidelines table for dabrafenib and trametinib combination; 6) Revised guidelines for handfoot skin reactions; 7) Revised management and dose modification guidelines for renal insufficiency; 8) Revised management and dose modification guidelines for pyrexia to remove blood sample for cytokine analysis; 9) Added new guidelines for pancreatitis and hyperglycemia; 10) Revised guidelines for visual changes for the dabrafenib and trametinib combination therapy arm to replace CSR with retinal pigment epithelium detachment and align with asset standard language.
07 August 2014	Protocol Amendment 5: 1) Revised medical monitors; 2) Revised study design to allow subjects randomized to the vemurafenib treatment the option to crossover to the dabrafenib and trametinib combination arm and included new Time and Events Table for crossover subjects; 3) Revised requirement for subjects who have been permitted to continue on study treatment after disease progression; 4) Revised and/or clarified the following dose modification guidelines based on emerging data to improve the management of adverse events: LVEF, cuSCC, new primary melanoma, non-cutaneus malignancies, pyrexia, renal insufficiency, visual changes, pancreatitis, and pneumonitis; 5) Based on emerging data, updated list of concomitant medications and clarified that oral contraceptives are not permitted for use as contraceptives; 6) Revised and/or clarified protocol-specific SAEs; 7) Clarified treatment of study-treatment overdose regarding hemodialysis; 8) Minor administrative changes, including formatting and re numbering of tables
22 July 2016	Protocol Amendment 6: 1) Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship; 2) Make administrative changes to align with Novartis processes and procedures
07 November 2017	Protocol Amendment 7: 1) Reduced RECIST v1.1 assessments after Week 56; from “every 12 weeks” to “as clinically indicated (at least every 24 weeks)”; 2) Increased the contraception requirement for male participants from 12 to 16 weeks in the period following stopping of study treatment. 4. Clarified that the lesion assessment scan were no longer collected for central review after 17 April 2014 (interim analysis cutoff date). All the scans were collected and assessed by the Investigator only since 23 April 2015.

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.

New malignancies and AEs possibly related to study treatment were collected even if they occurred more than 30 days post-treatment.

Notes: