Clinical trial results:
A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma

Summary

EudraCT number	2011-006087-49
Trial protocol	SE DE ES GB NL GR IT
Global end of trial date	28 February 2019

Results information

Result version number	v2 (current)
This version publication date	09 April 2021
First version publication date	14 March 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	115306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01584648
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharma AG, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Novartis Pharma AG, 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	28 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to establish the superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib placebo (dabrafenib monotherapy) with respect to progression free survival (PFS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

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 May 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	Argentina: 2
Country: Number of subjects enrolled	Australia: 40
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Ukraine: 22
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	423
EEA total number of subjects	244

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)	305
From 65 to 84 years	115
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 103 centers in 14 countries worldwide: Argentina (1), Australia (6), Canada (5), France (8), Germany (25), Greece (3), Italy (8), Netherlands (3), Russia (4), Spain (7), Sweden (4), Ukraine (7), United Kingdom (10), and USA (12).

Pre-assignment

Screening details:

Approximately, 340 subjects were planned to be randomized in a 1:1 ratio (170 subjects each in combination therapy and monotherapy). A total of 423 subjects with unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma were randomized to dabrafenib and trametinib (n=211) or dabrafenib and placebo (n=212).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabrafenib + Trametinib

Arm description:

Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued 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

Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	GSK1120212
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Trametinib 2 mg once daily

Arm title	Dabrafenib + Placebo

Arm description:

Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.

Arm type	Active comparator

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

Investigational medicinal product name	Trametinib placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib 150 mg twice daily and trametinib placebo

Number of subjects in period 1	Dabrafenib + Trametinib	Dabrafenib + Placebo
Started	211	212
Safety Set	209	211
Crossover Population	0	28
Completed	0	0
Not completed	211	212
Adverse event, serious fatal	136	146
Study closed/terminated	50	23
Crossover to Dabrafenib + Trametinib	-	28
Lost to follow-up	9	9
Investigator discretion	3	2
Withdrew consent	13	4

Baseline characteristics

Reporting groups	
Reporting group title	Dabrafenib + Trametinib
Reporting group description:	
Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Dabrafenib + Placebo
Reporting group description:	
Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	

Reporting group values	Dabrafenib + Trametinib	Dabrafenib + Placebo	Total
Number of subjects	211	212	423
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)	154	151	305
From 65-84 years	55	60	115
85 years and over	2	1	3
Sex: Female, Male Units:			
Female	100	98	198
Male	111	114	225
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	0	1	1
White - White/Caucasian/European Heritage	211	211	422
AgeContinuous Units: Years			
arithmetic mean	55.1	55.3	
standard deviation	± 13.33	± 13.75	-

End points

End points reporting groups

Reporting group title	Dabrafenib + Trametinib

Reporting group description:

Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Dabrafenib + Placebo

Reporting group description:

Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.

Subject analysis set title	Crossover Dabrafenib + Trametinib
Subject analysis set type	Safety analysis

Subject analysis set description:

Crossover Dabrafenib + Trametinib

Primary: Progression-Free Survival (PFS) as assessed by the investigator

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

End point description:

PFS is defined as the interval between the date of randomization and the earliest date of PD or death due to any cause. PD was based on radiographic or photographic evidence, and assessments were made by the investigator according to RECIST, version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. The appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation, was also included as PD. Participants who received anti-cancer therapy prior to the date of documented events, were censored at the last adequate assessment prior to the initiation of therapy. If the participant did not have documented progression or death, PFS was censored at the date of the last adequate assessment.

End point type	Primary

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 + Trametinib	Dabrafenib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	212		
Units: Months				
median (confidence interval 95%)	10.2 (8.1 to 12.8)	8.8 (5.9 to 9.3)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Comparison groups	Dabrafenib + Trametinib v Dabrafenib + Placebo
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.91

Secondary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description:	
OS is defined as the interval of time between the date of randomization and the date of death due to any cause. For the participants who did not die, overall survival was censored at the date of last contact.	
End point type	Secondary
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 + Trametinib	Dabrafenib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	212		
Units: Months				
median (confidence interval 95%)	25.8 (19.2 to 38.2)	18.7 (15.2 to 23.1)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Dabrafenib + Trametinib v Dabrafenib + Placebo
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.02

Secondary: Objective Response Rate (ORR) as assessed by the investigator

End point title	Objective Response Rate (ORR) as assessed by the investigator

End point description:

ORR is defined as the percentage of participants with a confirmed complete response (CR) or partial response (PR). A participant was defined as a responder if he/she sustained a complete response (CR: the disappearance of all target lesions and any pathological lymph nodes must have a short axis of <10 mm and the disappearance of all non-target lesions) or partial response (PR: at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters or the persistence of 1 or more non-target lesions or lymph nodes identified as a site of disease at Baseline with a short axis of ≥10mm). Only descriptive analysis performed.

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 + Trametinib	Dabrafenib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	210		
Units: Participants	146	113		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

Duration of response is defined as the time from the first documented complete response (CR: the disappearance of all target lesions and any pathological lymph nodes must have a short axis of <10 mm and the disappearance of all non-target lesions) or partial response (PR: at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters or the persistence of 1 or more non-target lesions or lymph nodes identified as a site of disease at Baseline with a short axis of ≥10mm) until disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5mm or the appearance of one or more new lesions, or the worsening of non target lesions significant enough to require study treatment discontinuation. PD was based on the radiological evidence by investigator. Only descriptive analysis performed.

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 + Trametinib	Dabrafenib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	114		
Units: Months				
median (confidence interval 95%)	12.9 (9.3 to 18.4)	10.2 (8.3 to 13.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events and Serious Adverse Events

End point title	Number of Participants with Adverse Events and Serious Adverse Events

End point description:

Analysis of absolute and relative frequencies for Adverse Event (AE) and Serious Adverse Event (SAE) by primary System Organ Class (SOC) to characterize the safety of dabrafenib and trametinib combination therapy through the monitoring of relevant clinical and laboratory safety parameters. In addition, new malignancies and AEs possibly related to study treatment were collected even if they occurred more than 30 days post-treatment. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From the time the first dose of study treatment administered until 30 days after discontinuation of study treatment (up to approximately 6 years).

End point values	Dabrafenib + Trametinib	Dabrafenib + Placebo	Crossover Dabrafenib + Trametinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	209	211	28	
Units: Participants				
Adverse Event (AEs)	203	205	24	
Serious Adverse Event (SAEs)	100	80	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Trametinib Pharmacokinetic Concentrations

End point title	Trametinib Pharmacokinetic Concentrations

End point description:

Blood samples were collected for Pharmacokinetic (PK) analysis in all participants. Three blood samples were collected at Week 8: pre-dose, 1-3 hours post dose, and 4-6 hours post dose. One pre-dose blood sample was obtained at Weeks 16 and 24. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Week 8 (0, 1-3, 4-6 hours post dose), Weeks 16 and 24 (0 hour pre-dose)

End point values	Dabrafenib + Trametinib	Dabrafenib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	194		
Units: Nanogram per Milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Week 8, pre-dose	9.9209 (± 3.86587)	0.0000 (± 0.00000)		
Week 8, 1-3 hours	19.0382 (± 6.86542)	0.0261 (± 0.34598)		
Week 8, 4-6 hours	16.7496 (± 5.64363)	0.0000 (± 0.00000)		
Week 16 pre-dose	11.0385 (± 4.79185)	0.0039 (± 0.03548)		
Week 24 pre-dose	11.5167 (± 5.19171)	0.0548 (± 0.62447)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dabrafenib and Dabrafenib Metabolites (Hydroxy-, Carboxy- and Desmethyl-Dabrafenib) Concentrations

End point title	Dabrafenib and Dabrafenib Metabolites (Hydroxy-, Carboxy- and Desmethyl-Dabrafenib) Concentrations

End point description:

Blood samples were collected for PK analysis in all participants. Three blood samples were collected at Week 8: pre-dose, 1-3 hours post dose, and 4-6 hours post dose. One pre-dose blood sample was obtained at Weeks 16 and 24. Plasma concentrations of Dabrafenib (GSK2118436) and its metabolites (Hydroxy-Dabrafenib (GSK2285403), Carboxy-Dabrafenib (GSK2298683), and Desmethyl-Dabrafenib (GSK2167542)) were determined using the currently approved analytical methodology. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Week 8 (0, 1-3, 4-6 hours post dose), Weeks 16 and 24 (0 hour pre-dose)

End point values	Dabrafenib + Trametinib	Dabrafenib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	194		
Units: Nanogram per Milliliter (ng/mL)				
arithmetic mean (standard deviation)				
GSK2118436, Week 8, pre-dose	92.1 (± 204.85)	64.4 (± 96.98)		

GSK2118436, Week 8, 1-3 hours	1309.6 (± 982.25)	1362.3 (± 992.97)		
GSK2118436, Week 8, 4-6 hours	458.9 (± 318.59)	539.7 (± 553.09)		
GSK2118436, Week 16 pre-dose	151.6 (± 261.31)	151.02 (± 381.32)		
GSK2118436, Week 24 pre-dose	167.0 (± 346.97)	156.5 (± 357.50)		
GSK2285403, Week 8, pre-dose	346.6 (± 261.73)	308.9 (± 224.56)		
GSK2285403, Week 8, 1-3 hours	361.7 (± 245.92)	341.8 (± 240.96)		
GSK2285403, Week 8, 4-6 hours	316.9 (± 208.51)	328.1 (± 234.95)		
GSK2285403, Week 16 pre-dose	335.0 (± 228.26)	331.0 (± 250.04)		
GSK2285403, Week 24 pre-dose	306.2 (± 203.77)	312.8 (± 250.28)		
GSK2298683, Week 8, pre-dose	82.0 (± 123.93)	76.7 (± 109.09)		
GSK2298683,Week 8, 1-3 hours	648.5 (± 459.01)	672.7 (± 519.45)		
GSK2298683, Week 8, 4-6 hours	391.3 (± 206.70)	502.2 (± 356.72)		
GSK2298683, Week 16 pre-dose	128.7 (± 174.26)	121.1 (± 195.15)		
GSK2298683,Week 24 pre-dose	126.1 (± 219.82)	145.7 (± 265.57)		
GSK2167542, Week 8, pre-dose	3237.2 (± 1694.66)	3469.4 (± 1854.02)		
GSK2167542, Week 8, 1-3 hours	4286.3 (± 2514.50)	4456.6 (± 2687.32)		
GSK2167542, Week 8, 4-6 hours	6238.3 (± 2716.05)	6891.6 (± 2739.07)		
GSK2167542, Week 16 pre-dose	3842.4 (± 2428.74)	4114.1 (± 2432.72)		
GSK2167542, Week 24 pre-dose	3617.9 (± 2645.51)	4193.2 (± 2730.78)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

Pre-treatment deaths were collected from screening visit up to the first day of treatment, for a maximum duration of 28 days. Patients who died during the screening period are considered as screen failure.
On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 77.4 months (treatment duration ranged from 0.1 to 76.4 months).
Deaths post treatment survival follow up were collected after the on- treatment period, up to approximately 6 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.

End point type	Post-hoc

End point timeframe:

up to 28 days before Day 1 (Screening), up to 77.4 months (on-treatment), up to approximately 6 years (study duration)

End point values	Dabrafenib + Trametinib	Dabrafenib + Placebo	Crossover Dabrafenib + Trametinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	210	211	28	
Units: Participants				
Pre-treatment deaths	1	0	0	
On-treatment deaths	29	25	0	
Post-treatment deaths	106	121	5	
All deaths	136	146	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit	
Adverse event reporting additional description:	
Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Dabrafenib + Trametinib
Reporting group description:	
Dabrafenib + Trametinib	
Reporting group title	Dabrafenib + Placebo
Reporting group description:	
Dabrafenib + Placebo	
Reporting group title	Crossover Dabrafenib + Trametinib
Reporting group description:	
Crossover Dabrafenib + Trametinib	
Reporting group title	All Patients
Reporting group description:	
All Patients	

Serious adverse events	Dabrafenib + Trametinib	Dabrafenib + Placebo	Crossover Dabrafenib + Trametinib
Total subjects affected by serious adverse events			
subjects affected / exposed	100 / 209 (47.85%)	80 / 211 (37.91%)	8 / 28 (28.57%)
number of deaths (all causes)	135	146	5
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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	8 / 209 (3.83%)	14 / 211 (6.64%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	11 / 13	13 / 18	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct adenocarcinoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Bowen's disease			
subjects affected / exposed	2 / 209 (0.96%)	2 / 211 (0.95%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Hodgkin's disease			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Keratoacanthoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Lipofibroma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Malignant melanoma			

subjects affected / exposed	1 / 209 (0.48%)	2 / 211 (0.95%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteosarcoma			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Phaeochromocytoma			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Prostate cancer			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Schwannoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Squamous cell carcinoma			
subjects affected / exposed	3 / 209 (1.44%)	7 / 211 (3.32%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	3 / 3	7 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 209 (0.96%)	15 / 211 (7.11%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	4 / 4	15 / 17	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage unspecified			

subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Hypertension			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hypotension			
subjects affected / exposed	6 / 209 (2.87%)	2 / 211 (0.95%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	3 / 7	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Thrombophlebitis superficial			

subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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	10 / 209 (4.78%)	3 / 211 (1.42%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	12 / 12	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drowning			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Fatigue			
subjects affected / exposed	3 / 209 (1.44%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 209 (1.44%)	0 / 211 (0.00%)	0 / 28 (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
Influenza like illness			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Malaise			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Pyrexia			

subjects affected / exposed	36 / 209 (17.22%)	15 / 211 (7.11%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	59 / 59	16 / 17	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Dyspnoea			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Nasal polyps			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Pleural effusion			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 209 (1.44%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory depression			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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	3 / 209 (1.44%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Mania			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Organic brain syndrome			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 209 (1.44%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Ejection fraction decreased			
subjects affected / exposed	13 / 209 (6.22%)	5 / 211 (2.37%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	12 / 17	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forced expiratory volume decreased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Oxygen saturation decreased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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 function test abnormal			

subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
White blood cell count decreased			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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			
Humerus fracture			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Joint dislocation			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Ligament rupture			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Ligament sprain			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Meniscus injury			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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 persistent drain fluid			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Radius fracture			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Upper limb fracture			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Atrial fibrillation			
subjects affected / exposed	3 / 209 (1.44%)	2 / 211 (0.95%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 209 (0.00%)	2 / 211 (0.95%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Myocardial infarction			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Tachycardia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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 oedema			
subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Central nervous system lesion			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Dizziness			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Epilepsy			
subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Facial paralysis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hemiplegia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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 disorder			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Paraesthesia			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Sciatica			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Syncope			
subjects affected / exposed	4 / 209 (1.91%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 209 (2.39%)	3 / 211 (1.42%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 209 (0.00%)	2 / 211 (0.95%)	0 / 28 (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
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hypochromic anaemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Neutropenia			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Pancytopenia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Thrombocytopenia			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (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			
Chorioretinopathy			
subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Iridocyclitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Uveitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Visual impairment			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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 disorders			
Abdominal pain			
subjects affected / exposed	4 / 209 (1.91%)	2 / 211 (0.95%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Acute abdomen			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Colitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Diarrhoea			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Intestinal perforation			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Jejunal perforation			

subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Nausea			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (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
Pancreatitis acute			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Peritoneal haemorrhage			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Rectal haemorrhage			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Vomiting			

subjects affected / exposed	3 / 209 (1.44%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haematoma			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Dermatosis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hyperhidrosis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hyperkeratosis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Skin lesion			

subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Skin ulcer			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Azotaemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Hydronephrosis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Nephritis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Pelvi-ureteric obstruction			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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			
Back pain			
subjects affected / exposed	0 / 209 (0.00%)	2 / 211 (0.95%)	0 / 28 (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
Compartment syndrome			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Haemarthrosis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hypercreatinaemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Immunoglobulin G4 related disease			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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 degeneration			

subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Muscle haemorrhage			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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	2 / 209 (0.96%)	1 / 211 (0.47%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Cystitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Febrile infection			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Kidney infection			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Laryngitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Neutropenic sepsis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Peritonitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Pneumonia			
subjects affected / exposed	6 / 209 (2.87%)	2 / 211 (0.95%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 6	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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	1 / 209 (0.48%)	1 / 211 (0.47%)	0 / 28 (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
Septic shock			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Staphylococcal sepsis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Superinfection			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 209 (0.96%)	1 / 211 (0.47%)	0 / 28 (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
Urosepsis			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 209 (0.48%)	2 / 211 (0.95%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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
Hyperglycaemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Hypoglycaemia			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	0 / 28 (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
Hypokalaemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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	0 / 209 (0.00%)	1 / 211 (0.47%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 28 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 28 (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

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	183 / 420 (43.57%)		
number of deaths (all causes)	286		
number of deaths resulting from adverse events	1		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	22 / 420 (5.24%)		
occurrences causally related to treatment / all	24 / 31		
deaths causally related to treatment / all	0 / 0		
Bile duct adenocarcinoma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Bowen's disease			
subjects affected / exposed	5 / 420 (1.19%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hodgkin's disease			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Keratoacanthoma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Lipofibroma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	3 / 420 (0.71%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Osteosarcoma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Phaeochromocytoma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Schwannoma			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	11 / 420 (2.62%)		
occurrences causally related to treatment / all	10 / 12		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			

subjects affected / exposed	18 / 420 (4.29%)			
occurrences causally related to treatment / all	19 / 22			
deaths causally related to treatment / all	0 / 0			
Superficial spreading melanoma stage unspecified				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	9 / 420 (2.14%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis superficial				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	13 / 420 (3.10%)			
occurrences causally related to treatment / all	16 / 16			
deaths causally related to treatment / all	0 / 0			
Drowning				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fatigue				
subjects affected / exposed	4 / 420 (0.95%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	3 / 420 (0.71%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	51 / 420 (12.14%)			
occurrences causally related to treatment / all	77 / 78			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Contrast media allergy				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Uterine prolapse				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	4 / 420 (0.95%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory depression			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 420 (0.95%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Organic brain syndrome			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	4 / 420 (0.95%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	19 / 420 (4.52%)			
occurrences causally related to treatment / all	18 / 23			
deaths causally related to treatment / all	0 / 0			
Forced expiratory volume decreased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oxygen saturation decreased				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal function test abnormal				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural persistent drain fluid				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	5 / 420 (1.19%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	3 / 420 (0.71%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiovascular insufficiency				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Aphasia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Central nervous system lesion				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral haemorrhage				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cerebral infarction				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dizziness				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiplegia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	5 / 420 (1.19%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	8 / 420 (1.90%)			
occurrences causally related to treatment / all	1 / 9			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haemolytic uraemic syndrome				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypochromic anaemia				

subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 420 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	2 / 420 (0.48%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Iridocyclitis			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	6 / 420 (1.43%)		
occurrences causally related to treatment / all	2 / 8		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute abdomen			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 420 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jejunal perforation				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritoneal haemorrhage				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 420 (0.71%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic haematoma				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis allergic				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatosis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperhidrosis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperkeratosis				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin lesion				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Azotaemia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephritis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvi-ureteric obstruction				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Compartment syndrome				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemarthrosis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercreatinaemia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immunoglobulin G4 related disease				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc degeneration				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscle haemorrhage				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	3 / 420 (0.71%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	8 / 420 (1.90%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 1			
Pseudomonas infection				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Superinfection				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 420 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 420 (0.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 420 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	4 / 420 (0.95%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 420 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 420 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 420 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dabrafenib + Trametinib	Dabrafenib + Placebo	Crossover Dabrafenib + Trametinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 209 (92.82%)	200 / 211 (94.79%)	23 / 28 (82.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 209 (0.96%)	16 / 211 (7.58%)	0 / 28 (0.00%)
occurrences (all)	3	20	0
Seborrhoeic keratosis			
subjects affected / exposed	12 / 209 (5.74%)	22 / 211 (10.43%)	0 / 28 (0.00%)
occurrences (all)	13	31	0
Skin papilloma			
subjects affected / exposed	6 / 209 (2.87%)	46 / 211 (21.80%)	1 / 28 (3.57%)
occurrences (all)	9	81	1
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 209 (3.83%)	5 / 211 (2.37%)	2 / 28 (7.14%)
occurrences (all)	9	5	2
Hypertension			
subjects affected / exposed	51 / 209 (24.40%)	33 / 211 (15.64%)	2 / 28 (7.14%)
occurrences (all)	76	42	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 209 (13.88%)	30 / 211 (14.22%)	4 / 28 (14.29%)
occurrences (all)	45	38	9
Chest pain			
subjects affected / exposed	12 / 209 (5.74%)	5 / 211 (2.37%)	0 / 28 (0.00%)
occurrences (all)	14	6	0
Chills			
subjects affected / exposed	63 / 209 (30.14%)	34 / 211 (16.11%)	3 / 28 (10.71%)
occurrences (all)	218	59	7
Fatigue			
subjects affected / exposed	79 / 209 (37.80%)	79 / 211 (37.44%)	7 / 28 (25.00%)
occurrences (all)	107	99	7

Influenza like illness			
subjects affected / exposed	17 / 209 (8.13%)	12 / 211 (5.69%)	3 / 28 (10.71%)
occurrences (all)	58	17	21
Oedema peripheral			
subjects affected / exposed	48 / 209 (22.97%)	17 / 211 (8.06%)	2 / 28 (7.14%)
occurrences (all)	72	19	2
Pain			
subjects affected / exposed	14 / 209 (6.70%)	9 / 211 (4.27%)	1 / 28 (3.57%)
occurrences (all)	14	9	1
Pyrexia			
subjects affected / exposed	118 / 209 (56.46%)	63 / 211 (29.86%)	10 / 28 (35.71%)
occurrences (all)	441	111	47
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 209 (0.48%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	51 / 209 (24.40%)	46 / 211 (21.80%)	3 / 28 (10.71%)
occurrences (all)	73	63	8
Dyspnoea			
subjects affected / exposed	16 / 209 (7.66%)	19 / 211 (9.00%)	1 / 28 (3.57%)
occurrences (all)	21	20	1
Epistaxis			
subjects affected / exposed	21 / 209 (10.05%)	11 / 211 (5.21%)	1 / 28 (3.57%)
occurrences (all)	44	15	1
Oropharyngeal pain			
subjects affected / exposed	24 / 209 (11.48%)	11 / 211 (5.21%)	0 / 28 (0.00%)
occurrences (all)	31	20	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 209 (5.74%)	6 / 211 (2.84%)	3 / 28 (10.71%)
occurrences (all)	12	7	3
Depression			
subjects affected / exposed	9 / 209 (4.31%)	12 / 211 (5.69%)	1 / 28 (3.57%)
occurrences (all)	9	12	1

Insomnia			
subjects affected / exposed	11 / 209 (5.26%)	18 / 211 (8.53%)	1 / 28 (3.57%)
occurrences (all)	15	21	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	25 / 209 (11.96%)	12 / 211 (5.69%)	1 / 28 (3.57%)
occurrences (all)	31	13	1
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 209 (13.88%)	8 / 211 (3.79%)	0 / 28 (0.00%)
occurrences (all)	36	8	0
Blood alkaline phosphatase increased			
subjects affected / exposed	18 / 209 (8.61%)	8 / 211 (3.79%)	3 / 28 (10.71%)
occurrences (all)	19	11	4
Blood creatine phosphokinase increased			
subjects affected / exposed	8 / 209 (3.83%)	0 / 211 (0.00%)	2 / 28 (7.14%)
occurrences (all)	10	0	3
Blood creatinine increased			
subjects affected / exposed	8 / 209 (3.83%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	9	4	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	8 / 209 (3.83%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	11	2	2
Ejection fraction decreased			
subjects affected / exposed	7 / 209 (3.35%)	2 / 211 (0.95%)	3 / 28 (10.71%)
occurrences (all)	7	2	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 209 (2.87%)	5 / 211 (2.37%)	4 / 28 (14.29%)
occurrences (all)	6	6	4
Neutrophil count decreased			
subjects affected / exposed	7 / 209 (3.35%)	0 / 211 (0.00%)	2 / 28 (7.14%)
occurrences (all)	8	0	7
Weight decreased			
subjects affected / exposed	13 / 209 (6.22%)	19 / 211 (9.00%)	0 / 28 (0.00%)
occurrences (all)	15	19	0

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 209 (2.87%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	9	2	3
Tendon rupture			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 209 (0.96%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	2	2	2
Tachycardia			
subjects affected / exposed	6 / 209 (2.87%)	13 / 211 (6.16%)	3 / 28 (10.71%)
occurrences (all)	8	13	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 209 (15.31%)	15 / 211 (7.11%)	1 / 28 (3.57%)
occurrences (all)	42	24	3
Dysgeusia			
subjects affected / exposed	6 / 209 (2.87%)	13 / 211 (6.16%)	2 / 28 (7.14%)
occurrences (all)	7	14	2
Headache			
subjects affected / exposed	71 / 209 (33.97%)	63 / 211 (29.86%)	6 / 28 (21.43%)
occurrences (all)	165	128	9
Paraesthesia			
subjects affected / exposed	9 / 209 (4.31%)	12 / 211 (5.69%)	1 / 28 (3.57%)
occurrences (all)	9	13	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 209 (7.66%)	22 / 211 (10.43%)	3 / 28 (10.71%)
occurrences (all)	21	23	3
Leukopenia			
subjects affected / exposed	7 / 209 (3.35%)	1 / 211 (0.47%)	2 / 28 (7.14%)
occurrences (all)	7	1	3
Neutropenia			

subjects affected / exposed	20 / 209 (9.57%)	5 / 211 (2.37%)	3 / 28 (10.71%)
occurrences (all)	26	5	6
Thrombocytopenia			
subjects affected / exposed	9 / 209 (4.31%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	9	2	2
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	5 / 209 (2.39%)	2 / 211 (0.95%)	3 / 28 (10.71%)
occurrences (all)	5	2	3
Eye disorders			
Blepharitis			
subjects affected / exposed	2 / 209 (0.96%)	0 / 211 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	2
Cataract			
subjects affected / exposed	2 / 209 (0.96%)	4 / 211 (1.90%)	3 / 28 (10.71%)
occurrences (all)	3	5	4
Dry eye			
subjects affected / exposed	11 / 209 (5.26%)	4 / 211 (1.90%)	1 / 28 (3.57%)
occurrences (all)	15	6	1
Vision blurred			
subjects affected / exposed	10 / 209 (4.78%)	5 / 211 (2.37%)	3 / 28 (10.71%)
occurrences (all)	10	7	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	29 / 209 (13.88%)	17 / 211 (8.06%)	1 / 28 (3.57%)
occurrences (all)	57	22	3
Abdominal pain upper			
subjects affected / exposed	20 / 209 (9.57%)	12 / 211 (5.69%)	3 / 28 (10.71%)
occurrences (all)	29	13	4
Constipation			
subjects affected / exposed	27 / 209 (12.92%)	22 / 211 (10.43%)	3 / 28 (10.71%)
occurrences (all)	33	25	7
Diarrhoea			
subjects affected / exposed	67 / 209 (32.06%)	34 / 211 (16.11%)	9 / 28 (32.14%)
occurrences (all)	149	53	12
Dry mouth			

subjects affected / exposed	18 / 209 (8.61%)	6 / 211 (2.84%)	1 / 28 (3.57%)
occurrences (all)	18	7	1
Nausea			
subjects affected / exposed	79 / 209 (37.80%)	57 / 211 (27.01%)	7 / 28 (25.00%)
occurrences (all)	175	89	11
Vomiting			
subjects affected / exposed	57 / 209 (27.27%)	31 / 211 (14.69%)	3 / 28 (10.71%)
occurrences (all)	134	48	3
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	12 / 209 (5.74%)	15 / 211 (7.11%)	1 / 28 (3.57%)
occurrences (all)	35	23	1
Alopecia			
subjects affected / exposed	19 / 209 (9.09%)	61 / 211 (28.91%)	0 / 28 (0.00%)
occurrences (all)	20	64	0
Dermatitis acneiform			
subjects affected / exposed	21 / 209 (10.05%)	8 / 211 (3.79%)	0 / 28 (0.00%)
occurrences (all)	25	9	0
Dry skin			
subjects affected / exposed	30 / 209 (14.35%)	33 / 211 (15.64%)	3 / 28 (10.71%)
occurrences (all)	36	37	3
Eczema			
subjects affected / exposed	19 / 209 (9.09%)	8 / 211 (3.79%)	2 / 28 (7.14%)
occurrences (all)	23	8	2
Erythema			
subjects affected / exposed	24 / 209 (11.48%)	16 / 211 (7.58%)	1 / 28 (3.57%)
occurrences (all)	31	17	1
Hair texture abnormal			
subjects affected / exposed	0 / 209 (0.00%)	18 / 211 (8.53%)	0 / 28 (0.00%)
occurrences (all)	0	18	0
Hyperhidrosis			
subjects affected / exposed	14 / 209 (6.70%)	9 / 211 (4.27%)	1 / 28 (3.57%)
occurrences (all)	43	11	1
Hyperkeratosis			
subjects affected / exposed	18 / 209 (8.61%)	79 / 211 (37.44%)	3 / 28 (10.71%)
occurrences (all)	27	145	3

Night sweats			
subjects affected / exposed	12 / 209 (5.74%)	5 / 211 (2.37%)	1 / 28 (3.57%)
occurrences (all)	13	7	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	11 / 209 (5.26%)	39 / 211 (18.48%)	2 / 28 (7.14%)
occurrences (all)	17	44	2
Pruritus			
subjects affected / exposed	28 / 209 (13.40%)	30 / 211 (14.22%)	2 / 28 (7.14%)
occurrences (all)	43	36	2
Rash			
subjects affected / exposed	62 / 209 (29.67%)	45 / 211 (21.33%)	3 / 28 (10.71%)
occurrences (all)	114	61	3
Rash maculo-papular			
subjects affected / exposed	13 / 209 (6.22%)	8 / 211 (3.79%)	3 / 28 (10.71%)
occurrences (all)	20	13	3
Skin lesion			
subjects affected / exposed	13 / 209 (6.22%)	10 / 211 (4.74%)	0 / 28 (0.00%)
occurrences (all)	17	15	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 209 (1.44%)	2 / 211 (0.95%)	2 / 28 (7.14%)
occurrences (all)	3	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	57 / 209 (27.27%)	68 / 211 (32.23%)	6 / 28 (21.43%)
occurrences (all)	100	102	15
Back pain			
subjects affected / exposed	30 / 209 (14.35%)	34 / 211 (16.11%)	3 / 28 (10.71%)
occurrences (all)	41	35	4
Muscle spasms			
subjects affected / exposed	19 / 209 (9.09%)	7 / 211 (3.32%)	3 / 28 (10.71%)
occurrences (all)	31	7	3
Muscular weakness			
subjects affected / exposed	5 / 209 (2.39%)	4 / 211 (1.90%)	2 / 28 (7.14%)
occurrences (all)	5	4	2
Musculoskeletal chest pain			

subjects affected / exposed	14 / 209 (6.70%)	11 / 211 (5.21%)	0 / 28 (0.00%)
occurrences (all)	15	12	0
Musculoskeletal pain			
subjects affected / exposed	12 / 209 (5.74%)	19 / 211 (9.00%)	1 / 28 (3.57%)
occurrences (all)	13	19	1
Myalgia			
subjects affected / exposed	27 / 209 (12.92%)	28 / 211 (13.27%)	3 / 28 (10.71%)
occurrences (all)	34	32	3
Pain in extremity			
subjects affected / exposed	34 / 209 (16.27%)	38 / 211 (18.01%)	3 / 28 (10.71%)
occurrences (all)	45	55	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 209 (5.74%)	8 / 211 (3.79%)	1 / 28 (3.57%)
occurrences (all)	15	9	1
Cystitis			
subjects affected / exposed	11 / 209 (5.26%)	2 / 211 (0.95%)	0 / 28 (0.00%)
occurrences (all)	30	3	0
Folliculitis			
subjects affected / exposed	12 / 209 (5.74%)	11 / 211 (5.21%)	2 / 28 (7.14%)
occurrences (all)	21	14	4
Influenza			
subjects affected / exposed	17 / 209 (8.13%)	7 / 211 (3.32%)	5 / 28 (17.86%)
occurrences (all)	27	11	6
Nasopharyngitis			
subjects affected / exposed	28 / 209 (13.40%)	21 / 211 (9.95%)	4 / 28 (14.29%)
occurrences (all)	53	34	6
Upper respiratory tract infection			
subjects affected / exposed	16 / 209 (7.66%)	7 / 211 (3.32%)	1 / 28 (3.57%)
occurrences (all)	25	7	1
Urinary tract infection			
subjects affected / exposed	29 / 209 (13.88%)	7 / 211 (3.32%)	2 / 28 (7.14%)
occurrences (all)	50	9	2
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	30 / 209 (14.35%)	28 / 211 (13.27%)	5 / 28 (17.86%)
occurrences (all)	38	30	7
Hyponatraemia			
subjects affected / exposed	5 / 209 (2.39%)	1 / 211 (0.47%)	2 / 28 (7.14%)
occurrences (all)	5	2	2

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	394 / 420 (93.81%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	18 / 420 (4.29%)		
occurrences (all)	23		
Seborrhoeic keratosis			
subjects affected / exposed	34 / 420 (8.10%)		
occurrences (all)	44		
Skin papilloma			
subjects affected / exposed	52 / 420 (12.38%)		
occurrences (all)	91		
Vascular disorders			
Hot flush			
subjects affected / exposed	15 / 420 (3.57%)		
occurrences (all)	16		
Hypertension			
subjects affected / exposed	85 / 420 (20.24%)		
occurrences (all)	122		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	60 / 420 (14.29%)		
occurrences (all)	92		
Chest pain			
subjects affected / exposed	17 / 420 (4.05%)		
occurrences (all)	20		
Chills			
subjects affected / exposed	98 / 420 (23.33%)		
occurrences (all)	284		

Fatigue			
subjects affected / exposed	161 / 420 (38.33%)		
occurrences (all)	213		
Influenza like illness			
subjects affected / exposed	31 / 420 (7.38%)		
occurrences (all)	96		
Oedema peripheral			
subjects affected / exposed	66 / 420 (15.71%)		
occurrences (all)	93		
Pain			
subjects affected / exposed	23 / 420 (5.48%)		
occurrences (all)	24		
Pyrexia			
subjects affected / exposed	183 / 420 (43.57%)		
occurrences (all)	599		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 420 (1.19%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	97 / 420 (23.10%)		
occurrences (all)	144		
Dyspnoea			
subjects affected / exposed	36 / 420 (8.57%)		
occurrences (all)	42		
Epistaxis			
subjects affected / exposed	33 / 420 (7.86%)		
occurrences (all)	60		
Oropharyngeal pain			
subjects affected / exposed	35 / 420 (8.33%)		
occurrences (all)	51		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	21 / 420 (5.00%)		
occurrences (all)	22		

Depression			
subjects affected / exposed	22 / 420 (5.24%)		
occurrences (all)	22		
Insomnia			
subjects affected / exposed	30 / 420 (7.14%)		
occurrences (all)	37		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	38 / 420 (9.05%)		
occurrences (all)	45		
Aspartate aminotransferase increased			
subjects affected / exposed	37 / 420 (8.81%)		
occurrences (all)	44		
Blood alkaline phosphatase increased			
subjects affected / exposed	29 / 420 (6.90%)		
occurrences (all)	34		
Blood creatine phosphokinase increased			
subjects affected / exposed	10 / 420 (2.38%)		
occurrences (all)	13		
Blood creatinine increased			
subjects affected / exposed	12 / 420 (2.86%)		
occurrences (all)	15		
Blood lactate dehydrogenase increased			
subjects affected / exposed	12 / 420 (2.86%)		
occurrences (all)	15		
Ejection fraction decreased			
subjects affected / exposed	12 / 420 (2.86%)		
occurrences (all)	12		
Gamma-glutamyltransferase increased			
subjects affected / exposed	14 / 420 (3.33%)		
occurrences (all)	16		
Neutrophil count decreased			
subjects affected / exposed	9 / 420 (2.14%)		
occurrences (all)	15		

Weight decreased			
subjects affected / exposed	32 / 420 (7.62%)		
occurrences (all)	34		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 420 (2.38%)		
occurrences (all)	14		
Tendon rupture			
subjects affected / exposed	3 / 420 (0.71%)		
occurrences (all)	3		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 420 (1.43%)		
occurrences (all)	6		
Tachycardia			
subjects affected / exposed	21 / 420 (5.00%)		
occurrences (all)	24		
Nervous system disorders			
Dizziness			
subjects affected / exposed	47 / 420 (11.19%)		
occurrences (all)	69		
Dysgeusia			
subjects affected / exposed	21 / 420 (5.00%)		
occurrences (all)	23		
Headache			
subjects affected / exposed	138 / 420 (32.86%)		
occurrences (all)	302		
Paraesthesia			
subjects affected / exposed	22 / 420 (5.24%)		
occurrences (all)	24		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 420 (9.05%)		
occurrences (all)	47		
Leukopenia			

subjects affected / exposed	10 / 420 (2.38%)		
occurrences (all)	11		
Neutropenia			
subjects affected / exposed	28 / 420 (6.67%)		
occurrences (all)	37		
Thrombocytopenia			
subjects affected / exposed	13 / 420 (3.10%)		
occurrences (all)	13		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	9 / 420 (2.14%)		
occurrences (all)	10		
Eye disorders			
Blepharitis			
subjects affected / exposed	4 / 420 (0.95%)		
occurrences (all)	4		
Cataract			
subjects affected / exposed	8 / 420 (1.90%)		
occurrences (all)	12		
Dry eye			
subjects affected / exposed	15 / 420 (3.57%)		
occurrences (all)	22		
Vision blurred			
subjects affected / exposed	18 / 420 (4.29%)		
occurrences (all)	20		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	47 / 420 (11.19%)		
occurrences (all)	82		
Abdominal pain upper			
subjects affected / exposed	35 / 420 (8.33%)		
occurrences (all)	46		
Constipation			
subjects affected / exposed	52 / 420 (12.38%)		
occurrences (all)	65		
Diarrhoea			

subjects affected / exposed	107 / 420 (25.48%)		
occurrences (all)	214		
Dry mouth			
subjects affected / exposed	24 / 420 (5.71%)		
occurrences (all)	26		
Nausea			
subjects affected / exposed	138 / 420 (32.86%)		
occurrences (all)	275		
Vomiting			
subjects affected / exposed	89 / 420 (21.19%)		
occurrences (all)	185		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	27 / 420 (6.43%)		
occurrences (all)	59		
Alopecia			
subjects affected / exposed	80 / 420 (19.05%)		
occurrences (all)	84		
Dermatitis acneiform			
subjects affected / exposed	29 / 420 (6.90%)		
occurrences (all)	34		
Dry skin			
subjects affected / exposed	65 / 420 (15.48%)		
occurrences (all)	76		
Eczema			
subjects affected / exposed	29 / 420 (6.90%)		
occurrences (all)	33		
Erythema			
subjects affected / exposed	41 / 420 (9.76%)		
occurrences (all)	49		
Hair texture abnormal			
subjects affected / exposed	18 / 420 (4.29%)		
occurrences (all)	18		
Hyperhidrosis			
subjects affected / exposed	23 / 420 (5.48%)		
occurrences (all)	55		

Hyperkeratosis			
subjects affected / exposed	97 / 420 (23.10%)		
occurrences (all)	175		
Night sweats			
subjects affected / exposed	17 / 420 (4.05%)		
occurrences (all)	21		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	50 / 420 (11.90%)		
occurrences (all)	63		
Pruritus			
subjects affected / exposed	59 / 420 (14.05%)		
occurrences (all)	81		
Rash			
subjects affected / exposed	109 / 420 (25.95%)		
occurrences (all)	178		
Rash maculo-papular			
subjects affected / exposed	24 / 420 (5.71%)		
occurrences (all)	36		
Skin lesion			
subjects affected / exposed	23 / 420 (5.48%)		
occurrences (all)	32		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	7 / 420 (1.67%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	127 / 420 (30.24%)		
occurrences (all)	217		
Back pain			
subjects affected / exposed	67 / 420 (15.95%)		
occurrences (all)	80		
Muscle spasms			
subjects affected / exposed	29 / 420 (6.90%)		
occurrences (all)	41		
Muscular weakness			

subjects affected / exposed	11 / 420 (2.62%)		
occurrences (all)	11		
Musculoskeletal chest pain			
subjects affected / exposed	25 / 420 (5.95%)		
occurrences (all)	27		
Musculoskeletal pain			
subjects affected / exposed	31 / 420 (7.38%)		
occurrences (all)	33		
Myalgia			
subjects affected / exposed	56 / 420 (13.33%)		
occurrences (all)	69		
Pain in extremity			
subjects affected / exposed	73 / 420 (17.38%)		
occurrences (all)	104		
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 420 (5.00%)		
occurrences (all)	25		
Cystitis			
subjects affected / exposed	13 / 420 (3.10%)		
occurrences (all)	33		
Folliculitis			
subjects affected / exposed	25 / 420 (5.95%)		
occurrences (all)	39		
Influenza			
subjects affected / exposed	28 / 420 (6.67%)		
occurrences (all)	44		
Nasopharyngitis			
subjects affected / exposed	50 / 420 (11.90%)		
occurrences (all)	93		
Upper respiratory tract infection			
subjects affected / exposed	24 / 420 (5.71%)		
occurrences (all)	33		
Urinary tract infection			
subjects affected / exposed	38 / 420 (9.05%)		
occurrences (all)	61		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	60 / 420 (14.29%)		
occurrences (all)	75		
Hyponatraemia			
subjects affected / exposed	8 / 420 (1.90%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2012	Amendment No. 01: 1. Included the statistical assumptions and analysis for the key secondary endpoint of OS. 2. Included 'incidence of squamous cell carcinoma" in the endpoints. 3. Included new requirements for subjects that remain on study treatment after radiographic disease progression 4. Allowed patients to continue on trametinib/placebo after discontinuation of dabrafenib so that patients may have the opportunity to potentially continue an active therapy that is not otherwise available 5. Required that study treatment will be interrupted for any treatment-related AE of Grade 3 6. Removed the use of topical steroids and topical/oral antibiotics from the prevention/prophylaxis of rash management for the first 28 days after study drug administration 7. Required that rash of ≥grade 3 must resolve to ≤grade 1 before study treatment can be restarted 8. Removed the allowance for palliative radiation and stated that subjects should not receive palliative radiotherapy prior to documented disease progression 9. Added an ophthalmic exam at week 4 to enhance the monitoring and more accurately assess the incidence of ophthalmic toxicities 10. Clarified that the LDH value collected within 14 days of randomization will be used for stratification 11. Required that the overall response rate and the duration of response be calculated using only confirmed (not unconfirmed) responses 12. Added bicarbonate and chloride to the clinical chemistry parameters 13. Added additional assessments at screening and discontinuation to monitor for second primary malignancies other than cutaneous SCC 14. Added assessments and a full skin examination to the brief physical exams 15. Included minor changes for clarification and consistency throughout the protocol
03 May 2012	Amendment No. 02: • Clarified: timings for ophthalmic exams and blood draws for cytokine analysis; requirements for cervical and rectal exams; acceptable toxicity levels for prior anti-cancer, treatment-related toxicities; requirements for whole-brain radiation; definition of asymptomatic hypertension, and definition of protocol specific SAE for new malignancies. • Added additional liver event follow up assessments to be consistent with GSK Oncology protocols. • Corrected typographical errors throughout and clerical errors in Appendix 8.
26 June 2012	Amendment No. 03: • A country-specific amendment as requested by the French regulatory agency to modify the QTc withholding criteria and to add valvular toxicity withholding criteria for subjects enrolled in France.

08 January 2013	Amendment No. 04: • Changed length of time contraception is required for males and females after permanently discontinuing study treatment based on emerging half-life data for trametinib. • Clarified that prothrombin time and partial thromboplastin time of >1.5 is acceptable at baseline for subjects receiving anticoagulant therapy. • Clarified that continuation of study treatment beyond radiographic (as defined by RECIST 1.1) or clinical disease progression may be possible. Note that this change does not affect the primary endpoint. • Clarified QTc stopping criteria. • Clarified collection frequency for blood samples for cytokine analysis. • Provided medical guidance for subjects with rigors/chills, but no fever. • Recommended that acetaminophen be used with caution in subjects with elevated liver enzymes. • Updated prohibited and cautionary medications. • Clarified that the informed consent may be signed >28 days prior to randomization. • Clarified that the Quality of Life assessment after disease progression also applies to subjects that have progressed but remain on study treatment. • Clarified assessments schedule for subjects that have withdrawn from study treatment prior to progression. • Removed language indicating that nodal lesions are measurable by X-ray. • Defined the intensity of hypotension required for a pyrexia-related SAE. • Performed clerical and administrative changes.
22 April 2013	Amendment No. 05: • Administrative changes including updated Sponsor Contact information. • Per FDA request, clarified criteria for allowing patients to continue study treatment after disease progression. • Updated concomitant medications based on emerging data.
20 May 2013	Amendment No. 06: • Updated the Data Analysis and Statistical Considerations (Section 9) to address the impact of over enrollment.
14 October 2013	Amendment No. 07: • As requested by the European Regulatory Authority, information for new malignancies will be collected throughout study treatment and follow-up. • As requested by French Regulatory Authority, additional monitoring following discontinuation of dabrafenib was incorporated • Administrative changes
12 August 2014	Amendment No. 08: • Administrative changes including updating medical monitors and formatting. • To obtain long-term survival data, increased the time to study closure. • To ensure optimum dosing, provided drug-specific instructions in cases where a dose is missed. • Based on emerging data, updated list of concomitant medications and stipulated that oral contraceptives are not permitted for use as contraceptives. • To improve management of adverse events, the following dose modification guidelines were modified and/or clarified based on emerging data: LVEF, HTN, QTc prolongation, hand-foot skin reactions, cuSCC, pyrexia, renal insufficiency, visual changes, and pneumonitis. Guidelines for new primary melanoma, non-cutaneous malignancies, pancreatitis, hyperglycemia, and retinal pigment epithelial detachment (RPED), which replaces the AE of CSR, were added. • Removed blood sample collection during pyrexic event for cytokine analysis as suffient sampling has been achieved. • Clarified treatment of study-treatment overdose regarding hemodialysis. • Due to the amount of censoring at the primary analysis, a descriptive analysis of PFS, DoR, and ORR will be conducted at the final analysis. • Based on feedback from the FDA, the final OS analysis will be performed at 220 events rather than 275. A descriptive OS update will be performed when 275 events have occurred. • To facilitate access to the combination therapy, text was added that will allow eligible subjects to crossover to the combination therapy if a statistically significant and clinically meaningful OS benefit is observed at the final OS analysis.

07 November 2016	Amendment No. 09: • Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. • Make administrative changes to align with Novartis processes and procedures.
27 November 2017	Amendment No. 10: • Reduce frequency of RECIST v1.1 assessments after Week 56; from "every 12 weeks" to "as clinically indicated (at least every 24 weeks)". • Clarify that the lesion assessment scan collection has been stopped for all scans performed after 12 January 2015 (interim analysis cutoff date) since 22 April 2015 • Add a contraception requirement for male participants. • Administrative changes: change Novartis staff names and contact details. Replace a reference to GSK, missed in previous amendment, with that of Novartis

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: