Clinical trial results:
An Open-Label, Multicenter Study to Assess the Safety of RO5185426 (Vemurafenib) in Patients with Metastatic Melanoma

Summary

EudraCT number	2010-023526-21
Trial protocol	ES AT SE NL SI GR DE GB CZ HU SK BE BG NO PT LV FI IT DK EE LT IE
Global end of trial date	24 February 2016

Results information

Result version number	v1 (current)
This version publication date	06 August 2017
First version publication date	06 August 2017

Trial information

Trial identification

Sponsor protocol code	MO25515

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01307397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of vemurafenib in participants with metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV, American Joint Committee on Cancer [AJCC]), harboring the BRAF V600 mutation (identified by the cobas® 4800 BRAF V600 Mutation Test)

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. Approval from the Ethics Committee (EC)/Institutional Review Board (IRB) was obtained before study start. Roche also obtained approval from the relevant Competent Authority prior to starting the study. No modifications were made to the protocol after receipt of the EC/IRB approval.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Albania: 12
Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	Australia: 158
Country: Number of subjects enrolled	Austria: 59
Country: Number of subjects enrolled	Belgium: 66
Country: Number of subjects enrolled	Bosnia and Herzegovina: 27
Country: Number of subjects enrolled	Brazil: 53
Country: Number of subjects enrolled	Bulgaria: 42
Country: Number of subjects enrolled	Canada: 145
Country: Number of subjects enrolled	Colombia: 17
Country: Number of subjects enrolled	Croatia: 21
Country: Number of subjects enrolled	Czech Republic: 137
Country: Number of subjects enrolled	Denmark: 28
Country: Number of subjects enrolled	Ecuador: 1
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	Germany: 389
Country: Number of subjects enrolled	Greece: 55

Country: Number of subjects enrolled	Hungary: 55
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Israel: 73
Country: Number of subjects enrolled	Italy: 383
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Lithuania: 13
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 20
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Netherlands: 234
Country: Number of subjects enrolled	Norway: 47
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Poland: 75
Country: Number of subjects enrolled	Portugal: 21
Country: Number of subjects enrolled	Romania: 29
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Serbia: 28
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Slovenia: 21
Country: Number of subjects enrolled	South Africa: 34
Country: Number of subjects enrolled	Spain: 300
Country: Number of subjects enrolled	Sweden: 77
Country: Number of subjects enrolled	Switzerland: 36
Country: Number of subjects enrolled	Turkey: 111
Country: Number of subjects enrolled	United Kingdom: 246
Worldwide total number of subjects	3219
EEA total number of subjects	2366

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)	3
Adults (18-64 years)	2371
From 65 to 84 years	825
85 years and over	20

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 7495 participants were screened; 3224 participants were enrolled and 3219 participants received at least 1 dose of vemurafenib. Further 38 participants were screened at a site in Austria and 29 of these participants were enrolled and treated; however, they were not included in analysis populations due to critical audit findings.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Vemurafenib

Arm description:

Participants received continuous oral doses of vemurafenib 960 milligrams (mg) (four 240 mg tablets) twice daily in each 28-day treatment cycle until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violations endangering participant's safety, death or study termination by the Sponsor.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO5185426, Zelboraf
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received continuous oral doses of vemurafenib 960 mg (four 240 mg tablets) twice daily in each 28-day treatment cycle until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violations endangering participant's safety, death or study termination by the Sponsor.

Number of subjects in period 1	Vemurafenib
Started	3219
Completed	0
Not completed	3219
Consent withdrawn by subject	62
Investigator's Decision	62
Death	120
Refused Treatment	66
Progressive Disease	2414
Administrative/Other	226
Adverse Events	225

Lost to follow-up	34
Missing	4
Protocol deviation	6

Baseline characteristics

Reporting groups	
Reporting group title	Vemurafenib
Reporting group description:	
Participants received continuous oral doses of vemurafenib 960 milligrams (mg) (four 240 mg tablets) twice daily in each 28-day treatment cycle until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violations endangering participant's safety, death or study termination by the Sponsor.	

Reporting group values	Vemurafenib	Total	
Number of subjects	3219	3219	
Age categorical Units: Subjects			

Age Continuous			
The safety population included all participants who received at least one dose of study medication			
Units: years			
arithmetic mean	54.5		
standard deviation	± 14.06	-	
Gender, Male/Female Units: Subjects			
Female	1397	1397	
Male	1822	1822	

End points

End points reporting groups

Reporting group title	Vemurafenib

Reporting group description:

Participants received continuous oral doses of vemurafenib 960 milligrams (mg) (four 240 mg tablets) twice daily in each 28-day treatment cycle until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violations endangering participant's safety, death or study termination by the Sponsor.

Primary: Percentage of Participants Experiencing Any Grade 3 or 4 Adverse Events (AEs) as determined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 4.0

End point title	Percentage of Participants Experiencing Any Grade 3 or 4 Adverse Events (AEs) as determined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 4.0[1]

End point description:

The intensity of AEs were graded on a 5-point scale (Grade 1 to 5) according to the NCI-CTCAE version 4.0, where Grade
1 indicates "Mild" severity and Grade 5 indicates "Death". The CTCAE defines Grades 3 and 4 as follows: Grade 3 means
"Severe"; Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the participant at direct risk. Grade 4 means "Life-threatening, Disabling"; based on extreme limitation in activity; significant medical intervention/therapy required; and hospitalization probable. Analysis was performed on the safety population (all participants who received at least one dose of study medication).

End point type	Primary

End point timeframe:

Baseline up to 28 days post end of treatment (maximum up to 46 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of participants				
number (not applicable)	52.8			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With at Least 1 AE Leading to Study Drug Interruption or Drug Discontinuation

End point title	Percentage of Participants With at Least 1 AE Leading to Study Drug Interruption or Drug Discontinuation[2]

End point description:

An AE was considered as any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Pre existing conditions that worsened during the study and laboratory or clinical tests that resulted in a change in treatment or discontinuation from study drug were reported as adverse events. Percentage of participants with dose interruption or discontinuation due to AE was presented. Analysis was performed on the safety population.

End point type	Primary

End point timeframe:

Baseline up to 28 days post end of treatment (maximum up to 46 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of participants				
number (not applicable)				
AE Leading to Drug Discontinuation	7			
AE Leading to Study Drug Interruption	34			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with AEs of Special Interest

End point title	Percentage of Participants with AEs of Special Interest[3]

End point description:

AEs of special interest included cutaneous squamous cell carcinoma (SCC), rash, photosensitivity, liver injury, arthralgia, fatigue, gastrointestinal (GI) polyps, pancreatitis, Potentiation of radiation toxicity, prolongation of cardiac repolarization or arrhythmia, non-cutaneous SCC and other primary malignancies (other than cutaneous SCC or new primary melanoma). Analysis was performed on the safety population.

End point type	Primary

End point timeframe:

Baseline up to 28 days post end of treatment (maximum up to 46 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of participants				
number (not applicable)				
Arthralgia	42.3			
Rash	47.9			
Photosensitivity	28.4			

Fatigue	36.8			
Cutaneous SCC	14.6			
Non Cutaneous SCC	0.1			
New Primary Melanoma	1.7			
GI Polyps	0.03			
Pancreatitis	0.2			
Potentiation of radiation toxicity	1.4			
Prolongation of Cardiac Repolarization/ Arrhythmia	17			
Other primary malignancy	3.2			
Liver Injury	14.1			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Cumulative Dose of Vemurafenib

End point title	Mean Cumulative Dose of Vemurafenib[4]

End point description:

Analysis was performed on the safety population.

End point type	Primary

End point timeframe:

Baseline up to end of treatment or death (maximum up to 46 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Grams				
arithmetic mean (standard deviation)	501.283 (± 510.9121)			

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Vemurafenib Treatment

End point title	Duration of Vemurafenib Treatment[5]

End point description:

Exposure excluding treatment interruptions: Duration during which participants actually took vemurafenib. Any time without dose taken due to adverse events, noncompliance or any other reasons was not counted. Exposure including treatment interruptions: date of last dose date of first dose + 1; duration during which participants actually took vemurafenib as well as duration on which medication was not taken were included in this calculation. Analysis was performed on the safety population.

End point type	Primary

End point timeframe:

Baseline up to end of treatment or death (maximum up to 46 months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Months				
arithmetic mean (standard deviation)				
Exposure excluding interruptions	9.383 (± 9.6755)			
Exposure including interruptions	9.724 (± 9.9072)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Total Vemurafenib Dose Per Day

End point title	Mean Total Vemurafenib Dose Per Day[6]

End point description:

Exposure excluding treatment interruptions: Duration during which participants actually took vemurafenib. Any time without dose taken due to adverse events, noncompliance or any other reasons was not counted. Exposure including treatment interruptions: date of last dose date of first dose + 1; duration during which participants actually took vemurafenib as well as duration on which medication was not taken were included in this calculation. Average total dose per day: total actual dose taken divided by total actual days on treatment. Analysis was performed on the safety population.

End point type	Primary

End point timeframe:

Baseline up to end of treatment or death (maximum up to 46 months)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Grams				
arithmetic mean (standard deviation)				
Average Total Dose Per Day Excluding Interruptions	1.802 (± 0.2314)			
Average Total Dose Per Day Including Interruptions	1.732 (± 0.2874)			

Statistical analyses

No statistical analyses for this end point

Primary: Dose Intensity of vemurafenib

End point title	Dose Intensity of vemurafenib[7]

End point description:

Dose intensity was defined as (total actual doses taken/total planned doses) *100, where total planned doses = prescribed doses * planned days on treatment, where planned days on treatment were defined as the interval between date of first dose and date of last dose. Analysis was performed on the safety population.

End point type	Primary

End point timeframe:

Baseline up to end of treatment or death (maximum up to 46 months)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis testing was done in this single arm Safety study. All results presented are descriptive only.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of planned dose				
arithmetic mean (standard deviation)	90.21 (± 14.966)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Improvement in Eastern Cooperative Group (ECOG) Performance Status

End point title	Percentage of Participants With Improvement in Eastern Cooperative Group (ECOG) Performance Status

End point description:

ECOG Performance Status was measured on therapy assessed participant's performance status on 5 point scale: 0 = fully active/able to carry on all pre disease activities without restriction; 1=restricted in physically strenuous activity, ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50% of waking hours [hrs]), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hrs; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead. Percentage of participants who had at least one point improvement from baseline at any assessment visit as well as at last study visit was reported. Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each 28 day cycle up to end of treatment (up to 46 months)

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of Participants				
number (not applicable)				
At Least 1 Point Improvement at Any Visit	24.7			
At Least 1 Point Improvement at Last Visit	9.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Received any Concomitant Medications

End point title	Percentage of Participants who Received any Concomitant Medications

End point description:

Concomitant medications were all medications taken during the study, including those started before but ongoing at first dose. No medications for Melanoma were included. Percentage of participants who received at least one concomitant medication was reported. Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Baseline up to 46 months

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of Participants				
number (not applicable)	93.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Response (BOR) of Confirmed Complete Response or Partial Response, as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Percentage of Participants With Best Overall Response (BOR) of Confirmed Complete Response or Partial Response, as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point description:

BOR was assessed by the investigator according to RECIST v1.1. BOR was defined as having confirmed CR or PR. CR: disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to less than (<) 10 millimeter (mm) in short axis; PR: at least a 30%

decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesion, and no new lesions. Confirmed responses were those that persisted on repeat imaging greater than or equal to (>=) 4 weeks after initial response. Analysis was performed on the safety population. Number of subjects analyzed = participants with measurable disease at baseline

End point type	Secondary

End point timeframe:

Baseline until first documentation of confirmed CR or PR (assessed at baseline, at Weeks 8, 16, as per institution standard of care thereafter but a minimum every 16 weeks thereafter until the end of the study [up to 46 months])

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	2982			
Units: Percentage of Participants				
number (confidence interval 95%)	33.4 (31.7 to 35.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

The duration of response was defined as the time between the date of first confirmed CR or PR and date of first progression of disease (PD), or death, from any cause. Responses were assessed as per RECIST v1.1. CR: disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to < 10 mm in short axis; PR: at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesion, and no new lesions. Confirmed responses were those that persisted on repeat imaging >= 4 weeks after initial response. PD: at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on study and absolute increase of at least 5 mm, progression of existing non target lesions, or presence of new lesion. Analysis was performed on the safety population. Number of subjects analyzed=participants who achieved CR or PR.

End point type	Secondary

End point timeframe:

From 1st documentation of confirmed CR or PR to PD or death, whichever occurred first (assessed at baseline, at Weeks 8, 16, as per institution standard of care thereafter but a minimum every 16 weeks thereafter until end of the study [up to 46 months])

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	996			
Units: Months				
median (confidence interval 95%)	7.4 (7.1 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time between the date of first treatment and date of first confirmed CR or PR (assessed as per RECIST v1.1). CR: disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to < 10 mm in short axis; PR: at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesion, and no new lesions. Confirmed responses were those that persisted on repeat imaging >= 4 weeks after initial response. Analysis was performed on the safety population. Number of subjects analyzed = participants with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Baseline until first documentation of confirmed CR or PR, whichever occurred first (assessed at baseline, at Weeks 8, 16,
as per institution standard of care thereafter but a minimum every 16 weeks thereafter until the end of the study [up to 46
months])

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	2982			
Units: Months				
median (full range (min-max))	1.84 (0.8 to 26.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PD Assessed According to RECIST v1.1 or Death

End point title	Percentage of Participants With PD Assessed According to RECIST v1.1 or Death

End point description:

PD was assessed according to RECIST v1.1. PD was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesion. Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Baseline until PD or death, whichever occurred first (assessed at baseline, at Weeks 8, 16, as per institution standard of care thereafter but a minimum every 16 weeks thereafter until the end of the study [up to 46 months])

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of Participants				
number (not applicable)	87.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time between the date of the first treatment and the date of first progression or death from any cause. PD was assessed according to RECIST v1.1. PD was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesion. Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Baseline until PD or death, whichever occurred first (assessed at baseline, at Weeks 8, 16, as per institution standard of care thereafter but a minimum every 16 weeks thereafter until the end of the study [up to 46 months])

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Months				
median (confidence interval 95%)	5.6 (5.5 to 5.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Baseline until death (maximum up to 46 months)

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Percentage of participants				
number (not applicable)	63.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival was defined as the time from the date of first treatment to the date of death, regardless of the cause of death. Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Baseline until death (maximum up to 46 months)

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	3219			
Units: Months				
median (confidence interval 95%)	12.1 (11.5 to 12.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 28 days post end of treatment (maximum up to 46 months)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Vemurafenib

Reporting group description:

Participants received continuous oral doses of vemurafenib 960 mg (four 240 mg tablets) twice daily in each 28-day treatment cycle until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violations endangering participant's safety, death or study termination by the Sponsor.

Serious adverse events	Vemurafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	1114 / 3219 (34.61%)		
number of deaths (all causes)	2054		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	68 / 3219 (2.11%)		
occurrences causally related to treatment / all	68 / 79		
deaths causally related to treatment / all	0 / 0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial tumour haemorrhage			
subjects affected / exposed	7 / 3219 (0.22%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	2 / 3		
Fibrous histiocytoma			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Keratoacanthoma			
subjects affected / exposed	260 / 3219 (8.08%)		
occurrences causally related to treatment / all	359 / 361		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	43 / 3219 (1.34%)		
occurrences causally related to treatment / all	36 / 46		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma in situ			
subjects affected / exposed	10 / 3219 (0.31%)		
occurrences causally related to treatment / all	8 / 10		
deaths causally related to treatment / all	0 / 0		
Melanocytic naevus			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Mycosis Fungoides			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Papilloma			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Skin papilloma			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			

subjects affected / exposed	259 / 3219 (8.05%)		
occurrences causally related to treatment / all	348 / 352		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Tumour Ulceration			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour necrosis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acanthoma			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Adrenocarcinoma of Colon			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Benign Neoplasm of Skin			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bowen's Disease			
subjects affected / exposed	5 / 3219 (0.16%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Carcinoma In Situ of Skin			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cervix Carcinoma Stage 0			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholesteatoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chondrosarcoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ependymoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye Naevus			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infected Neoplasm			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intraductal Proliferative Breast Lesion			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kaposi's Sarcoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myxoid Liposarcoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine Carcinoma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine Carcinoma of the Skin			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine Tumour			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral Papilloma			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic Carcinoma			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal Cancer			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seborrhoeic Keratosis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin Neoplasm Bleeding			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma of the Oral Cavity			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma of the Vulva			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superficial Spreading Melanoma Stage Unspecified			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Synovial Sarcoma				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional Cell Carcinoma				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Tumour Associated Fever				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lentigo Maligna				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Intermittent Claudication				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extremity necrosis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypotension				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
thrombophlebitis				

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Circulatory Collapse				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Deep vein thrombosis				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertensive Crisis				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic fatigue syndrome				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Death			
subjects affected / exposed	7 / 3219 (0.22%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	1 / 7		
Drug Dislocation			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug interaction			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	6 / 3219 (0.19%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	9 / 3219 (0.28%)		
occurrences causally related to treatment / all	4 / 9		
deaths causally related to treatment / all	2 / 5		
Malaise			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Multi-organ disorder			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Multi-organ failure			

subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	2 / 2			
Oedema				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	32 / 3219 (0.99%)			
occurrences causally related to treatment / all	17 / 34			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Asthenia				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Generalised Oedema				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired Healing				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical Failure				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visceral Pain			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Euthanasia			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Food allergy			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Haemorrhage			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Adnexal Torsion				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial Hyperplasia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metrorrhagia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peyronie's Disease				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine cervical erosion				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chronic obstructive pulmonary disease				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Acute respiratory failure				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			

Dyspnoea			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	1 / 1		
Epistaxis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	6 / 3219 (0.19%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	13 / 3219 (0.40%)		
occurrences causally related to treatment / all	3 / 13		
deaths causally related to treatment / all	0 / 3		
Respiratory failure			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Pulmonary Oedema			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bronchial Haemorrhage			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
hydrothorax				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleurisy				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuritic Pain				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Toxicity				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Vocal Cord Leukoplakia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Completed suicide				

subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Confusional state				
subjects affected / exposed	5 / 3219 (0.16%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bipolar Disorder				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mood Altered				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Aspartate aminotransferase increased				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	7 / 3219 (0.22%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Gamma glutamyltransferase increased			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Blood glucose increased			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			

subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fall			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Over dose			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation injury			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory fume inhalation disorder			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis Radiation			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial Bone Fracture			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femur Fracture			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture Displacement			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head Injury			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Humerus Fracture			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar Vertrebral Fracture			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Multiple Injuries			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Patella Fracture			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation Necrosis			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Radius Fracture			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road Traffic Accident			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Compression Fracture			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic Rupture			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural Haematoma				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sunburn				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon Injury				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia Fracture				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to Various Agents				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	10 / 3219 (0.31%)			
occurrences causally related to treatment / all	1 / 10			
deaths causally related to treatment / all	1 / 4			
Angina pectoris				
subjects affected / exposed	5 / 3219 (0.16%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	15 / 3219 (0.47%)			
occurrences causally related to treatment / all	6 / 15			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	6 / 3219 (0.19%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Left ventricular dysfunction				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	7 / 3219 (0.22%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 2			
Pericardial effusion				
subjects affected / exposed	7 / 3219 (0.22%)			
occurrences causally related to treatment / all	4 / 7			
deaths causally related to treatment / all	0 / 0			
Pericardial haemorrhage				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	7 / 3219 (0.22%)		
occurrences causally related to treatment / all	7 / 8		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Torsade de pointes			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Acute Coronary Syndrome			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular Block			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina Unstable			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardiac Failure Acute			

subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac Faiure Congestive				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiogenic Shock				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cardiomyopathy				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Stenosis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus Node Dysfunction				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular Tachycardia				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				

subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Cerebral haemorrhage			
subjects affected / exposed	14 / 3219 (0.43%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	3 / 8		
Cognitive disorder			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	10 / 3219 (0.31%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 5		
Depressed Level of Consicousness			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dizziness			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	10 / 3219 (0.31%)		
occurrences causally related to treatment / all	1 / 14		
deaths causally related to treatment / all	0 / 0		
Generalised Tonic Clonic Seizure			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial paresis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Haemorrhagic stroke			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Headache			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Intracranial Pressure Increased			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Ischaemic stroke			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stupor			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIIth nerve paralysis			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Balance Disorder			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral Disorder			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrospinal Fluid Leakage			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Facial Nerve Disorder			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic Encephalopathy			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			

subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Monoplegia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurotoxicity				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Partial Seizures				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral Sensorimotor Neuropathy				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	12 / 3219 (0.37%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Simple Partial Seizure				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Compression				

subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Status Epilepticus				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachanoid Haemorrhage				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vasogenic Cerebral Oedema				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebellar Infarction				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	22 / 3219 (0.68%)			
occurrences causally related to treatment / all	7 / 25			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Eosinophilia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				

subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Agranulocytosis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Febrile Neutropenia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymph Node Pain				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Microcytic Anaemia				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Deafness				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vertigo				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hearnig Impaired				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Neovascular Age-related macular degeneration			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Iridocyclitis			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	6 / 3219 (0.19%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Macular Oedema			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Papilloedema			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Retinal Artery occlusion			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal Detachment			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinopathy			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iritis			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	6 / 3219 (0.19%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	16 / 3219 (0.50%)		
occurrences causally related to treatment / all	9 / 16		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Duodenal ulcer			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Heamatemesis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Jejunal perforation			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	13 / 3219 (0.40%)		
occurrences causally related to treatment / all	11 / 15		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	17 / 3219 (0.53%)			
occurrences causally related to treatment / all	9 / 18			
deaths causally related to treatment / all	0 / 0			
Anal Fistula				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Anal skin Tags				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enteroocolitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Faeces Pale			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Food Poisoning			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric Haemorrhagic			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Necrosis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal Toxicity			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal Ischaemia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intussusception			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukoplakia oral			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth Ulceration			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia oral			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal Haemorrhage				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haematoma				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				

subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	3 / 3219 (0.09%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatic Failure				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis Toxic				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Acanthosis				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Actinic keratosis				
subjects affected / exposed	9 / 3219 (0.28%)			
occurrences causally related to treatment / all	10 / 10			
deaths causally related to treatment / all	0 / 0			
Angioedema				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Dermatitis exfoliative				

subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity Vasculitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Photosensitivity reaction			
subjects affected / exposed	5 / 3219 (0.16%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	7 / 3219 (0.22%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	5 / 3219 (0.16%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Rash pruritic			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin Mass			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Toxic epidermal necrolysis			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 1		
Lichenoid Keratosis			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dermal Cyst			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis exfoliative Generalised			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug eruption			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Erythema Nodosum			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkeratosis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Panniculitis			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rash Erythematous			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash Follicular				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash Generalised				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rash Macular				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash Papular				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Steven Johnson Syndrome				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Calculus ureteric				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Glomerulonephritis minimal lesion				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal Colic				

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract disorder			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Kidney Injury			
subjects affected / exposed	8 / 3219 (0.25%)		
occurrences causally related to treatment / all	4 / 9		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nephropathy			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nephhropathy Toxic			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial Nephritis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Fistula			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperadrenalism			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 3219 (0.37%)		
occurrences causally related to treatment / all	11 / 13		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	6 / 3219 (0.19%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		

Myalgia				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoporosis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dupuytren's Contracture				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteitis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Pain				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess Limb			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	5 / 3219 (0.16%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Blastocystis infection			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	5 / 3219 (0.16%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	9 / 3219 (0.28%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Groin abscess			
subjects affected / exposed	5 / 3219 (0.16%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
H1N1 Influenza			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	7 / 3219 (0.22%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	6 / 3219 (0.19%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis externa			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal cyst			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pharyngotonsillitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	31 / 3219 (0.96%)			
occurrences causally related to treatment / all	4 / 39			
deaths causally related to treatment / all	1 / 3			
Pneumocystis jiroveci pneumonia				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Postoperative Wound Infection				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rash pustular				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	7 / 3219 (0.22%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 2			
Sepsis				
subjects affected / exposed	7 / 3219 (0.22%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	1 / 3			
Salmonella sepsis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	11 / 3219 (0.34%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	3 / 3219 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Vulvitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Wound infection staphylococcal			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acinetobacter Infection			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis Perforated			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis Bacterial			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain Abscess			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical Pneumonia			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Infective			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic Abscess			

subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Viral			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Infection			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypopyon			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected Dermal Cyst			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious Pleural Effusion			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised Infection			
subjects affected / exposed	2 / 3219 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymph Gland Infection			

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ophthalmic Herpes Zoster			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perineal Abscess			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin Bacterial Infection			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft Tissue Infection			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subdiaphragmatic Abscess			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth Abscess			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth Infection			

subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium Colitis				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				
subjects affected / exposed	1 / 3219 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	4 / 3219 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperuricaemia				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	2 / 3219 (0.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased Appetite			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	4 / 3219 (0.12%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Type 2 Diabestes Mellitus			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Electrolyte Imbalance			
subjects affected / exposed	1 / 3219 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 3219 (0.03%)		
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	Vemurafenib		
Total subjects affected by non-serious adverse events subjects affected / exposed	2956 / 3219 (91.83%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed	621 / 3219 (19.29%)		
occurrences (all)	953		
Melanocytic Naevus subjects affected / exposed	227 / 3219 (7.05%)		
occurrences (all)	332		
Seborrhoeic Keratosis subjects affected / exposed	266 / 3219 (8.26%)		
occurrences (all)	333		
Vascular disorders Hypertension subjects affected / exposed	264 / 3219 (8.20%)		
occurrences (all)	348		
General disorders and administration site conditions Fatigue subjects affected / exposed	834 / 3219 (25.91%)		
occurrences (all)	1129		
Pyrexia subjects affected / exposed	363 / 3219 (11.28%)		
occurrences (all)	484		
Asthenia subjects affected / exposed	382 / 3219 (11.87%)		
occurrences (all)	535		
Oedema Peripheral subjects affected / exposed	238 / 3219 (7.39%)		
occurrences (all)	274		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	191 / 3219 (5.93%)		
occurrences (all)	215		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	163 / 3219 (5.06%)		
occurrences (all)	175		
Investigations			
Weight decreased			
subjects affected / exposed	414 / 3219 (12.86%)		
occurrences (all)	485		
Electrocardiogram QT prolonged			
subjects affected / exposed	521 / 3219 (16.19%)		
occurrences (all)	753		
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	318 / 3219 (9.88%)		
occurrences (all)	522		
Nervous system disorders			
Headache			
subjects affected / exposed	458 / 3219 (14.23%)		
occurrences (all)	637		
Dysgeusia			
subjects affected / exposed	191 / 3219 (5.93%)		
occurrences (all)	205		
Blood and lymphatic system disorders			
Anaenia			
subjects affected / exposed	215 / 3219 (6.68%)		
occurrences (all)	316		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	584 / 3219 (18.14%)		
occurrences (all)	866		
Nausea			
subjects affected / exposed	718 / 3219 (22.31%)		
occurrences (all)	965		

Vomiting			
subjects affected / exposed	449 / 3219 (13.95%)		
occurrences (all)	635		
Constipation			
subjects affected / exposed	196 / 3219 (6.09%)		
occurrences (all)	211		
Abdominal Pain			
subjects affected / exposed	170 / 3219 (5.28%)		
occurrences (all)	214		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	873 / 3219 (27.12%)		
occurrences (all)	942		
Dry skin			
subjects affected / exposed	538 / 3219 (16.71%)		
occurrences (all)	597		
Erythema			
subjects affected / exposed	327 / 3219 (10.16%)		
occurrences (all)	415		
Hyperkeratosis			
subjects affected / exposed	830 / 3219 (25.78%)		
occurrences (all)	1201		
Photosensitivity reaction			
subjects affected / exposed	678 / 3219 (21.06%)		
occurrences (all)	891		
Pruritus			
subjects affected / exposed	320 / 3219 (9.94%)		
occurrences (all)	370		
Rash			
subjects affected / exposed	556 / 3219 (17.27%)		
occurrences (all)	709		
Palmar Plantar Erythrodysaesthesia syndrome			
subjects affected / exposed	193 / 3219 (6.00%)		
occurrences (all)	253		

Actinic Keratosis			
subjects affected / exposed	246 / 3219 (7.64%)		
occurrences (all)	405		
Rash Erythematous			
subjects affected / exposed	195 / 3219 (6.06%)		
occurrences (all)	246		
Rash Maculo- Papular			
subjects affected / exposed	179 / 3219 (5.56%)		
occurrences (all)	240		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1357 / 3219 (42.16%)		
occurrences (all)	2178		
Myalgia			
subjects affected / exposed	308 / 3219 (9.57%)		
occurrences (all)	402		
Back Pain			
subjects affected / exposed	191 / 3219 (5.93%)		
occurrences (all)	214		
Muscloskeletal Pain			
subjects affected / exposed	222 / 3219 (6.90%)		
occurrences (all)	277		
Pain in Extremity			
subjects affected / exposed	276 / 3219 (8.57%)		
occurrences (all)	343		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	170 / 3219 (5.28%)		
occurrences (all)	199		
Nasopharyngitis			
subjects affected / exposed	171 / 3219 (5.31%)		
occurrences (all)	223		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	482 / 3219 (14.97%)		
occurrences (all)	603		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2011	• Based on result of a different study similar participant population was allowed to be enrolled in this study and therefore participants with surgically incurable and unresectable Stage IIIC or Stage IV (AJCC) and participants who had not received prior treatment for metastatic melanoma were allowed into the study (in addition to participants who had received prior treatment). • Included participants at least 16 years of age due to the assumed similarities between the biological/physiological and pharmacokinetic/pharmacodynamic characteristics of 16 to 18-year-old participants. • Excluded participants with a known hypersensitivity to vemurafenib or another BRAF inhibitor. • Excluded participants with congenital long QT syndrome considering the recent data of effect of vemurafenib on the QT interval. • Clarified the type of concomitant medication that was prohibited or must be used with caution. • Included ECG monitoring to be 28 days after starting treatment with vemurafenib, every 4 weeks for the following 3 months, every 12 weeks thereafter and at the end of study/follow-up visit, following the new safety information. • Clarified the definition of the date at which the Screening Period started to be the date at which the first archival tumor tissue sample was sent to the central testing laboratory for BRAF mutation testing, except when a study procedure was performed prior to sending the tumor sample to the testing laboratory, when this date was recorded as the date of the start of Screening. • Clarified the reporting of SCC to allow for the proper coding to the preferred term cutaneous SCC and clarified that SCC should be reported as an serious AE only if it meets the definition of an serious AE.
30 November 2011	• Included a long term follow-up safety phase for 24 months after the last participant enrolled. • Added information to the study background. • Included tolerability as part of the primary objective of the study, together with safety. • Clearly defined the end of treatment visit and the 28 day follow-up visit after discontinuation of vemurafenib and updated the sections referring to visits. • Increased the number of participants to be screened and enrolled. • Clarified that only a protocol violation that endangered a participant's safety would mandate discontinuation of study treatment. • Added the option for participants who developed disease progression but who in the opinion of the investigator would still benefit from continuing vemurafenib treatment, could do so after discussion with the Sponsor. • Included that for participants who developed any other suspicious lesions (in addition to SCC), tissue from the lesions was also to be provided for confirmation of diagnosis by a designated central pathology laboratory. • Clarified when the study enrolment would end in relation to local regulatory approval and reimbursement of vemurafenib for the treatment of metastatic melanoma. • Increased the number of study centers. • Clarified the exclusion criteria • Clarified the use of limited field radiotherapy to include all palliative reasons if the limited field radiotherapy was not considered a target lesion for the RECIST assessments. • Increased the follow-up of chest CT for evaluation of non cutaneous SCC. • Clarified that the participants with known or suspected bone metastases should undergo radionuclide bone scan or PET scan at baseline if clinically indicated. • Clarified the definition of AE and SAEs. • Amended the statistical analyses.

15 August 2012	• Added that participant recruitment has been higher than expected with additional countries and sites than originally planned being included. The protocol has been updated to reflect the higher number of participant and revised statistical assumptions. It was estimated that approximately 7400 participants will be screened and approximately 3300 participants with the BRAF V600 mutation will be enrolled in the study and receive treatment with vemurafenib. • Increased the visit window to +/- 5 days to allow flexibility and to be more realistic to clinical routine, and the follow-up visit to after 28 days. • Included an additional head and neck examination for monitoring of non cutaneous SCCs to align with the monitoring guidance of the Zelboraf® (marketed name of vemurafenib) Summary of Product Characteristics, to the Long Term Safety Follow-up Phase, to be performed at 6 months following study drug discontinuation or until initiation of another neo plastic therapy. • Added a dermatological evaluation at 6 months following study drug discontinuation or until initiation of another anti neoplastic therapy for monitoring of cutaneous SCCs to align with the monitoring guidance of the vemurafenib Summary of Product Characteristics • Included for consistency throughout the protocol that as well as cutaneous SCC, BCC and keratoacanthoma and other second primary malignancies were defined as events requiring close monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported