



Clinical trial results:

A Phase III Double-blind, Placebo-controlled Study of Vemurafenib Versus Vemurafenib Plus GDC-0973 in Previously Untreated BRAF^{V600}-mutation Positive Patients With Unresectable Locally Advanced or Metastatic Melanoma

Summary

EudraCT number	2012-003008-11
Trial protocol	GB ES CZ AT NO DE BE SE IT NL HU FR
Global end of trial date	

Results information

Result version number	v3
This version publication date	14 August 2016
First version publication date	07 August 2015
Version creation reason	<ul style="list-style-type: none">New data added to full data set Updated data available

Trial information

Trial identification

Sponsor protocol code	GO28141
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01689519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, 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?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	30 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of vemurafenib in combination with cobimetinib (GDC-0973), compared with vemurafenib and placebo, in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by progression-free survival (PFS), assessed by the study site investigator.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 95
Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	New Zealand: 10
Worldwide total number of subjects	495
EEA total number of subjects	329

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	362
From 65 to 84 years	128
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Vemurafenib

Arm description:

Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 milligrams (mg) orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

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

Dosage and administration details:

Placebo orally once a day on days 1-21 of each 28-day treatment cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent.

Investigational medicinal product name	vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg orally twice a day on days 1-28 of each 28-day cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent.

Arm title	Cobimetinib + Vemurafenib
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Arm description:

Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Arm type	Experimental
Investigational medicinal product name	cobimetinib
Investigational medicinal product code	
Other name	GDC-0973
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg orally once a day on days 1-21 of each 28-day treatment cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent

Investigational medicinal product name	vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

960 mg orally twice a day on days 1-28 of each 28-day cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent

Number of subjects in period 1	Placebo + Vemurafenib	Cobimetinib + Vemurafenib
Started	248	247
Received Treatment	247	246
Completed	82	109
Not completed	166	138
Physician decision	-	3
Death	143	116
Lost to follow-up	6	2
Withdrawal by subject	17	17

Baseline characteristics

Reporting groups

Reporting group title	Placebo + Vemurafenib
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Reporting group description:

Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 milligrams (mg) orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group title	Cobimetinib + Vemurafenib
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Reporting group description:

Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib	Total
Number of subjects	248	247	495
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	55.3 ± 13.8	54.9 ± 14	-
Gender categorical Units: Subjects			
Female	108	101	209
Male	140	146	286

End points

End points reporting groups

Reporting group title	Placebo + Vemurafenib
Reporting group description: Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 milligrams (mg) orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.	
Reporting group title	Cobimetinib + Vemurafenib
Reporting group description: Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.	

Primary: Progression-free survival

End point title	Progression-free survival
End point description: Progression-free survival was defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors v1.1, or death from any cause, whichever came first. Disease progression was defined as: (1) at least a 20% increase in the sum (the increase in the sum must be at least 5 mm) of diameters of target lesions, taking as reference the smallest sum during the study; (2) unequivocal progression of existing non-target lesions; or (3) the appearance of 1 or more new lesions.	
Intent-to-treat population: All randomized subjects, regardless of whether or not study treatment was received.	
End point type	Primary
End point timeframe: Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247 ^[1]		
Units: months				
median (confidence interval 95%)	6.21 (5.55 to 7.39)	9.89 (9 to 999.99)		

Notes:

[1] - 999.99 = not estimable, could not be calculated due to too few events.

Statistical analyses

Statistical analysis title	Stratified analysis
Statistical analysis description: The analysis was stratified by geographic region and metastasis classification (disease stage).	
Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.512
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	0.679

Secondary: Overall survival

End point title	Overall survival
End point description:	
Overall survival was defined as the time from randomization until the date of death from any cause.	
Intent-to-treat population: All randomized subjects, regardless of whether or not study treatment was received.	
End point type	Secondary
End point timeframe:	
Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248 ^[2]	247 ^[3]		
Units: months				
median (confidence interval 95%)	999.99 (999.99 to 999.99)	999.99 (999.99 to 999.99)		

Notes:

[2] - 999.99 = not estimable, could not be calculated due to too few events.

[3] - 999.99 = not estimable, could not be calculated due to too few events.

Statistical analyses

Statistical analysis title	Stratified analysis
Statistical analysis description:	
The analysis was stratified by geographic region and metastasis classification (disease stage).	
Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0463
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.417
upper limit	0.996

Secondary: Percentage of subjects with an objective response

End point title	Percentage of subjects with an objective response
End point description:	
An objective response was defined as a complete response or a partial response determined on two consecutive occasions ≥ 4 weeks apart. Responses were determined by Response Evaluation Criteria in Solid Tumors v1.1. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter of target lesions.	
Intent-to-treat population: All randomized subjects, regardless of whether or not study treatment was received.	
End point type	Secondary
End point timeframe:	
Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247		
Units: percentage of participants				
number (confidence interval 95%)	44.8 (38.46 to 51.18)	67.6 (61.39 to 73.41)		

Statistical analyses

Statistical analysis title	Difference in objective response rates
Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	22.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.13
upper limit	31.58

Secondary: Duration of response

End point title	Duration of response
End point description:	
Duration of response was defined as the time from first occurrence of a documented confirmed objective response until the time of disease progression, as determined by investigator review of tumor assessments using Response Evaluation Criteria in Solid Tumors v1.1 or death from any cause during the study. Disease progression was defined as: (1) at least a 20% increase in the sum (the increase in the sum must be at least 5 mm) of diameters of target lesions, taking as reference the smallest sum during the study; (2) unequivocal progression of existing non-target lesions; or (3) the appearance of 1 or more new lesions.	
Intent-to-treat population: All randomized subjects, regardless of whether or not study treatment was received. Only subjects with an objective response were included in the analysis.	
End point type	Secondary
End point timeframe:	
Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111 ^[4]	167 ^[5]		
Units: months				
median (confidence interval 95%)	7.29 (5.78 to 999.99)	999.99 (9.3 to 999.99)		

Notes:

[4] - 999.99 = not estimable, could not be calculated due to too few events.

[5] - 999.99 = not estimable, could not be calculated due to too few events.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Final Analysis)

End point title	Overall Survival (Final Analysis)
End point description:	
Overall survival was defined as the time from randomization until the date of death from any cause.	

Intent-to-treat population: All randomized subjects, regardless of whether or not study treatment was received.

End point type	Secondary
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End point timeframe:

Baseline to the 28 August 2015 Overall Survival data cut-off (up to 2 years, 8 months)

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247 ^[6]		
Units: months				
median (confidence interval 95%)	17.38 (15.01 to 19.81)	22.28 (20.27 to 999.99)		

Notes:

[6] - 999.99 = not estimable, could not be calculated due to too few events.

Statistical analyses

Statistical analysis title	Stratified analysis
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Statistical analysis description:

The analysis was stratified by geographic region and metastasis classification (disease stage).

Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.702
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.548
upper limit	0.899

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of each participant's randomization into the study until their last visit until 28 days after the last dose of study drug (Safety data cut-off: 30 September 2015; up to 2 years, 9 months)

Adverse event reporting additional description:

Safety population: All subjects who received at least 1 dose of study treatment (ie, cobimetinib/placebo or vemurafenib).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo + Vemurafenib
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Reporting group description:

Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group title	Cobimetinib + Vemurafenib
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Reporting group description:

Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Serious adverse events	Placebo + Vemurafenib	Cobimetinib + Vemurafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 246 (28.05%)	92 / 247 (37.25%)	
number of deaths (all causes)	142	117	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acanthoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Benign neoplasm			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kaposi's sarcoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	4 / 246 (1.63%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucinous breast carcinoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia	subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
	occurrences causally related to treatment / all	0 / 0	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Death	subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
	occurrences causally related to treatment / all	0 / 1	0 / 1	
	deaths causally related to treatment / all	0 / 1	0 / 1	
Fatigue	subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
	occurrences causally related to treatment / all	0 / 0	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise	subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
	occurrences causally related to treatment / all	0 / 0	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	subjects affected / exposed	3 / 246 (1.22%)	6 / 247 (2.43%)	
	occurrences causally related to treatment / all	2 / 3	6 / 8	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders				
Hypersensitivity	subjects affected / exposed	0 / 246 (0.00%)	3 / 247 (1.21%)	
	occurrences causally related to treatment / all	0 / 0	3 / 3	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis	subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
	occurrences causally related to treatment / all	0 / 0	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders				
Cervical polyp	subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 246 (1.22%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	2 / 246 (0.81%)	4 / 247 (1.62%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 246 (0.81%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 246 (0.41%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 246 (0.41%)	4 / 247 (1.62%)	
occurrences causally related to treatment / all	1 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			

subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	4 / 246 (1.63%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			

subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysgeusia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 246 (0.00%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIIth nerve paralysis			

subjects affected / exposed	1 / 246 (0.41%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 246 (0.00%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iridocyclitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 246 (0.00%)	4 / 247 (1.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous ulcer			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 246 (0.00%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 246 (0.81%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontal disease			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 246 (0.00%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 246 (0.41%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema nodosum			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkeratosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Panniculitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 246 (0.41%)	4 / 247 (1.62%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	2 / 246 (0.81%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash morbilliform			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 246 (0.81%)	3 / 247 (1.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Clostridium difficile infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 246 (0.81%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 246 (0.81%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 246 (1.22%)	4 / 247 (1.62%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			

subjects affected / exposed	2 / 246 (0.81%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cellulitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 246 (0.00%)	5 / 247 (2.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Vemurafenib	Cobimetinib + Vemurafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	235 / 246 (95.53%)	238 / 247 (96.36%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	6 / 246 (2.44%)	15 / 247 (6.07%)	
occurrences (all)	6	28	
Keratoacanthoma			
subjects affected / exposed	20 / 246 (8.13%)	4 / 247 (1.62%)	
occurrences (all)	26	5	
Melanocytic naevus			
subjects affected / exposed	20 / 246 (8.13%)	5 / 247 (2.02%)	
occurrences (all)	31	5	
Seborrhoeic keratosis			
subjects affected / exposed	20 / 246 (8.13%)	15 / 247 (6.07%)	
occurrences (all)	21	15	
Skin papilloma			
subjects affected / exposed	31 / 246 (12.60%)	17 / 247 (6.88%)	
occurrences (all)	36	22	
Squamous cell carcinoma of skin			

subjects affected / exposed occurrences (all)	31 / 246 (12.60%) 64	10 / 247 (4.05%) 25	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	20 / 246 (8.13%) 22	38 / 247 (15.38%) 45	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	43 / 246 (17.48%) 47 13 / 246 (5.28%) 16 82 / 246 (33.33%) 99 28 / 246 (11.38%) 32 57 / 246 (23.17%) 71	46 / 247 (18.62%) 66 25 / 247 (10.12%) 28 91 / 247 (36.84%) 128 34 / 247 (13.77%) 44 69 / 247 (27.94%) 104	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	31 / 246 (12.60%) 35 18 / 246 (7.32%) 19 21 / 246 (8.54%) 27	23 / 247 (9.31%) 28 19 / 247 (7.69%) 24 18 / 247 (7.29%) 19	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	10 / 246 (4.07%) 11	13 / 247 (5.26%) 14	

Insomnia subjects affected / exposed occurrences (all)	24 / 246 (9.76%) 26	17 / 247 (6.88%) 22	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	43 / 246 (17.48%) 47	62 / 247 (25.10%) 87	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	29 / 246 (11.79%) 29	58 / 247 (23.48%) 78	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	24 / 246 (9.76%) 28	41 / 247 (16.60%) 55	
Blood bilirubin increased subjects affected / exposed occurrences (all)	17 / 246 (6.91%) 22	19 / 247 (7.69%) 21	
Blood cholesterol increased subjects affected / exposed occurrences (all)	10 / 246 (4.07%) 10	16 / 247 (6.48%) 16	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	7 / 246 (2.85%) 8	86 / 247 (34.82%) 134	
Blood creatinine increased subjects affected / exposed occurrences (all)	20 / 246 (8.13%) 23	37 / 247 (14.98%) 48	
Ejection fraction decreased subjects affected / exposed occurrences (all)	12 / 246 (4.88%) 14	28 / 247 (11.34%) 38	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	44 / 246 (17.89%) 60	52 / 247 (21.05%) 72	
Weight decreased subjects affected / exposed occurrences (all)	13 / 246 (5.28%) 15	16 / 247 (6.48%) 18	
Injury, poisoning and procedural			

complications			
Sunburn			
subjects affected / exposed	45 / 246 (18.29%)	37 / 247 (14.98%)	
occurrences (all)	66	57	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 246 (3.25%)	15 / 247 (6.07%)	
occurrences (all)	8	15	
Dysgeusia			
subjects affected / exposed	25 / 246 (10.16%)	38 / 247 (15.38%)	
occurrences (all)	26	42	
Headache			
subjects affected / exposed	39 / 246 (15.85%)	44 / 247 (17.81%)	
occurrences (all)	46	64	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 246 (8.13%)	39 / 247 (15.79%)	
occurrences (all)	24	50	
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	1 / 246 (0.41%)	29 / 247 (11.74%)	
occurrences (all)	2	34	
Retinal detachment			
subjects affected / exposed	1 / 246 (0.41%)	19 / 247 (7.69%)	
occurrences (all)	1	21	
Vision blurred			
subjects affected / exposed	6 / 246 (2.44%)	28 / 247 (11.34%)	
occurrences (all)	6	28	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 246 (7.32%)	26 / 247 (10.53%)	
occurrences (all)	19	31	
Abdominal pain upper			
subjects affected / exposed	17 / 246 (6.91%)	12 / 247 (4.86%)	
occurrences (all)	19	13	
Constipation			

subjects affected / exposed	28 / 246 (11.38%)	26 / 247 (10.53%)	
occurrences (all)	30	33	
Diarrhoea			
subjects affected / exposed	82 / 246 (33.33%)	149 / 247 (60.32%)	
occurrences (all)	136	275	
Dyspepsia			
subjects affected / exposed	14 / 246 (5.69%)	19 / 247 (7.69%)	
occurrences (all)	14	22	
Nausea			
subjects affected / exposed	64 / 246 (26.02%)	105 / 247 (42.51%)	
occurrences (all)	78	166	
Stomatitis			
subjects affected / exposed	3 / 246 (1.22%)	15 / 247 (6.07%)	
occurrences (all)	3	23	
Vomiting			
subjects affected / exposed	33 / 246 (13.41%)	63 / 247 (25.51%)	
occurrences (all)	41	97	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	25 / 246 (10.16%)	13 / 247 (5.26%)	
occurrences (all)	29	31	
Alopecia			
subjects affected / exposed	75 / 246 (30.49%)	41 / 247 (16.60%)	
occurrences (all)	78	43	
Dermatitis acneiform			
subjects affected / exposed	22 / 246 (8.94%)	34 / 247 (13.77%)	
occurrences (all)	26	42	
Dry skin			
subjects affected / exposed	41 / 246 (16.67%)	38 / 247 (15.38%)	
occurrences (all)	44	41	
Erythema			
subjects affected / exposed	33 / 246 (13.41%)	26 / 247 (10.53%)	
occurrences (all)	49	46	
Hyperkeratosis			
subjects affected / exposed	66 / 246 (26.83%)	25 / 247 (10.12%)	
occurrences (all)	113	33	

Keratosis pilaris			
subjects affected / exposed	26 / 246 (10.57%)	9 / 247 (3.64%)	
occurrences (all)	29	10	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	9 / 246 (3.66%)	17 / 247 (6.88%)	
occurrences (all)	10	21	
Palmoplantar keratoderma			
subjects affected / exposed	20 / 246 (8.13%)	5 / 247 (2.02%)	
occurrences (all)	21	6	
Photosensitivity reaction			
subjects affected / exposed	48 / 246 (19.51%)	84 / 247 (34.01%)	
occurrences (all)	56	115	
Pruritus			
subjects affected / exposed	47 / 246 (19.11%)	49 / 247 (19.84%)	
occurrences (all)	52	75	
Rash			
subjects affected / exposed	94 / 246 (38.21%)	98 / 247 (39.68%)	
occurrences (all)	117	151	
Rash maculo-papular			
subjects affected / exposed	37 / 246 (15.04%)	36 / 247 (14.57%)	
occurrences (all)	47	60	
Solar dermatitis			
subjects affected / exposed	13 / 246 (5.28%)	15 / 247 (6.07%)	
occurrences (all)	22	22	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	103 / 246 (41.87%)	94 / 247 (38.06%)	
occurrences (all)	168	150	
Back pain			
subjects affected / exposed	14 / 246 (5.69%)	19 / 247 (7.69%)	
occurrences (all)	14	23	
Musculoskeletal pain			
subjects affected / exposed	16 / 246 (6.50%)	11 / 247 (4.45%)	
occurrences (all)	18	12	
Myalgia			

subjects affected / exposed occurrences (all)	31 / 246 (12.60%) 34	36 / 247 (14.57%) 47	
Pain in extremity subjects affected / exposed occurrences (all)	39 / 246 (15.85%) 50	29 / 247 (11.74%) 45	
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	5 / 246 (2.03%) 5	16 / 247 (6.48%) 17	
Folliculitis subjects affected / exposed occurrences (all)	12 / 246 (4.88%) 15	18 / 247 (7.29%) 19	
Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 246 (5.69%) 16	20 / 247 (8.10%) 24	
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 246 (4.07%) 12	15 / 247 (6.07%) 18	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	50 / 246 (20.33%) 55	50 / 247 (20.24%) 62	
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 246 (1.22%) 3	13 / 247 (5.26%) 19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2012	Version 2 of the protocol included the following changes: correction of typographical errors; relocation of some text and minor editing for greater clarity.
24 April 2013	Version 3 of the protocol included the following changes: added PFS as assessed by independent review as a secondary endpoint; clarified exclusion criteria 4 to allow subjects with previously resected early stage melanoma into the study; added cardiac events/Grade ≥ 2 LVEF reduction as AESIs; revised guidelines for cases of emergency unblinding to allow investigators the ability to unblind without the Sponsor's approval; change in reporting windows for pregnancy and pregnant partners, for LVEF, dermatology, and ophthalmology exams after Cycle 2; revised guidelines on corrected QT interval (QTc) monitoring/cardiac consult to be more conservative; updated safety information on the cobimetinib plus vemurafenib combination; further clarified procedures described in the protocol to enhance readability and understanding; changed "GDC-0973" to "cobimetinib" throughout the document.
12 September 2013	Version 4 of the protocol included the following changes: updated safety information for consistency with the vemurafenib Investigator's Brochure; updated and further clarified procedures described in the protocol to enhance readability and understanding.
17 March 2014	Protocol Version 4 Addendum 1, In response to a request from Health Canada, the protocol was revised to include lipase and amylase testing to confirm diagnosis in suspected cases of pancreatitis. At this time, the Canadian addendum to the protocol has not been incorporated a global amendment and therefore has not been implemented globally.
24 February 2015	Version 5 of the protocol included the following changes: updated safety information on vemurafenib to include information on progression of cancers associated with RAS mutations, panniculitis, radiation recall/sensitization, and pancreatitis; updated risks associated with cobimetinib following the final efficacy analysis of this study and updates to the cobimetinib Investigator's Brochure (IB, Version 7). Following the final efficacy analysis and extensive evaluation of safety data, quarterly Data Safety and Monitoring Board review of unblinded safety data will no longer occur. Following the final efficacy analysis, quality of life assessments will no longer be conducted. Tumor assessments will be conducted in accordance with local standard of care. Central collection and review of tumor scans will no longer be required. The analysis plan for overall survival (OS) was revised, with final OS analysis to be performed at approximately 250 deaths without further interim analyses. Following the final efficacy analysis and evaluation of electrocardiogram (ECG) data, ECG monitoring requirements were revised. The Medical Monitor was changed.
20 October 2015	Version 6 of the protocol included the following changes: following the final overall survival analysis, there was a reduction of the schedule of dermatological, physical, anal, and gynecological exams, to align with the Investigator's Brochure for vemurafenib. Addition of high-level summary of results of the primary and final analyses of Study GO28141. Removal of the background pharmacokinetic data from Study N025395. Allowance for participants to cross over to treatment with vemurafenib / cobimetinib. Provision of a description of commercially available tablets and allowance for participants to switch to commercial supplies of study drug, when available. Change to the Medical Monitor contact information. Clarification that the source of Reference Safety Information for vemurafenib is the Investigator's Brochure and update of the safety data cutoff, where appropriate. Update of dose-modification guidelines modified to reflect practices to be applied during the course of standard clinical care.

30 March 2016	Version 7 of the protocol included the following changes: addition of safety information for vemurafenib related to acute kidney injury. Revision of safety information for cobimetinib, including the addition of the potential risk of rhabdomyolysis and/or Grade 4 increased creatine phosphokinase (CPK) and reorganization of risk section into Identified/Potential/Other risks associated with cobimetinib. Provision of further clarity for the crossover of treatment from placebo to cobimetinib, including the schedule for performing ophthalmologic examinations and evaluations of left ventricular function. Provision of further clarity around performance of safety assessments. Images for left ventricular function no longer were to be sent for central review. Reversion of dose modification language to Protocol Version 5, to remain consistent with usual practice. Removal of GDC-0973 from the protocol text and the use of cobimetinib throughout.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported