Clinical trial results:
COMBI-AD: A phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection

Summary

EudraCT number	2012-001266-15
Trial protocol	BE SE CZ DE NO GB AT GR IT NL DK ES
Global end of trial date	31 July 2023

Results information

Result version number	v1
This version publication date	25 July 2024
First version publication date	25 July 2024

Trial information

Trial identification

Sponsor protocol code	115532

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01682083
WHO universal trial number (UTN)	-
Other trial identifiers	legacy GSK code: BRF115532, Novartis: CDRB436F2301

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to Relapse Free Survival (RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K high-risk, stage III cutaneous melanoma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	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	Argentina: 5
Country: Number of subjects enrolled	Australia: 103
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	France: 109
Country: Number of subjects enrolled	Germany: 90
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 97
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Norway: 19

Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 69
Worldwide total number of subjects	870
EEA total number of subjects	505

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)	712
From 65 to 84 years	156
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 169 centers across 25 countries.

Pre-assignment

Screening details:

Patients were planned to be randomized in a 1:1 ratio, stratified by BRAF mutation status (V600E, V600K) and stage of disease (Stage IIIa, IIIb, IIIc).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabrafenib and Trametinib combination therapy

Arm description:

Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	GSK2118436
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib, 150 mg twice daily (bid) + trametinib, 2 mg (once daily). Dabrafenib was provided as 50 mg and 75 mg capsules. Each capsule contained 50 mg or 75 mg of free base (present as the mesylate salt).

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

Dosage and administration details:

Dabrafenib, 150 mg twice daily (bid) + trametinib, 2 mg (once daily). Trametinib study treatment was provided as 0.5 mg and 2 mg tablets. Each tablet contained 0.5 mg or 2 mg of trametinib parent (present as the dimethyl sulfoxide solvate).

Arm title	Dabrafenib and Trametinib placebos

Arm description:

Subjects received matching placebos orally for 12 months

Arm type	Placebo
Investigational medicinal product name	Matching placebo capsules for dabrafenib, 150 mg (bid) + placebo tablets for trametinib, 2 mg (once daily)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo capsules/tablets contained the same inactive ingredients and film coatings as the dabrafenib and trametinib study treatment.

Number of subjects in period 1	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos
Started	438	432
Untreated	3	0
Safety Population	435	432
Completed	0	0
Not completed	438	432
Adverse event, serious fatal	125	136
Physician decision	11	8
Consent withdrawn by subject	50	53
Study closed by sponsor	225	192
Lost to follow-up	27	43

Baseline characteristics

Reporting groups	
Reporting group title	Dabrafenib and Trametinib combination therapy
Reporting group description:	
Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months.	
Reporting group title	Dabrafenib and Trametinib placebos
Reporting group description:	
Subjects received matching placebos orally for 12 months	

Reporting group values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos	Total
Number of subjects	438	432	870
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	353	359	712
From 65-84 years	84	72	156
85 years and over	1	1	2
Age Continuous Units: Years			
arithmetic mean	50.4	50.5	
standard deviation	± 14.17	± 13.14	-
Sex: Female, Male Units: participants			
Female	195	193	388
Male	243	239	482
Race/Ethnicity, Customized Units: Subjects			
White	432	427	859
Asian	6	5	11

End points

End points reporting groups

Reporting group title	Dabrafenib and Trametinib combination therapy
Reporting group description:	
Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months.	
Reporting group title	Dabrafenib and Trametinib placebos
Reporting group description:	
Subjects received matching placebos orally for 12 months	

Primary: Relapse-free survival (RFS)

End point title	Relapse-free survival (RFS)
End point description:	
Recurrence-free survival was defined as the time from randomization to disease recurrence (local recurrence, distant recurrence, second primary melanoma), or death from any cause. Patients with no event by the time of the analysis cut-off date (30-Jun-2017) were censored at the date of the last efficacy assessment (i.e., either radiological or non-radiological) prior to the analysis cut-off. Patients lost to follow-up prior to disease recurrence were censored. Patients who started subsequent anti-cancer therapy prior to disease recurrence were censored at the date of last efficacy assessment (either radiological or non-radiological) before the initiation of subsequent anti-cancer therapy. Patients for whom an event occurred after a period of extended lost-to-follow-up were censored.	
End point type	Primary
End point timeframe:	
Approximately 3.5 years	

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Months				
median (full range (min-max))	999 (44.5 to 999)	16.6 (12.7 to 22.1)		

Statistical analyses

Statistical analysis title	Relapse-free survival (RFS)
Statistical analysis description:	
The null hypothesis, H0: $\lambda = 1$ or reject it in favor of the alternative hypothesis, HA: $\lambda \neq 1$, where λ is the hazard ratio (HR) of combination therapy relative to placebo.	
Comparison groups	Dabrafenib and Trametinib combination therapy v Dabrafenib and Trametinib placebos

Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.58

Primary: Percentage of Participants with Relapse-free survival (RFS) events

End point title	Percentage of Participants with Relapse-free survival (RFS) events[1]

End point description:

Patients with no event by the time of the analysis cut-off date (30-Jun-2017) were censored at the date of the last efficacy assessment (i.e., either radiological or non-radiological) prior to the analysis cut-off. Patients lost to follow-up prior to disease recurrence were censored.
Patients who started subsequent anti-cancer therapy prior to disease recurrence were censored at the date of last efficacy assessment (either radiological or non-radiological) before the initiation of subsequent anti-cancer therapy. Patients for whom an event occurred after a period of extended lost-to-follow-up were censored.

End point type	Primary

End point timeframe:

Approximately 3.5 years

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: Only descriptive statistics performed

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Participants				
Relapsed (event)	163	247		
Died (event)	3	1		
Censored, follow-up ended at Primary Completion	43	35		
Censored, follow-up ongoing at Primary Completion	229	149		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) was defined as the interval from randomization to the date of death, irrespective of the cause of death. Censoring was performed using the date of last known contact for those who were alive at the time of analysis.

End point type	Secondary

End point timeframe:

Approximately 10 years

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Months				
median (full range (min-max))	999 (120.7 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)

Statistical analysis description:

Hazard ratio is obtained from the stratified Pike estimator.

Comparison groups	Dabrafenib and Trametinib combination therapy v Dabrafenib and Trametinib placebos
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.063
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.01

Secondary: Percentage of Participants with Overall Survival (OS) events

End point title	Percentage of Participants with Overall Survival (OS) events

End point description:

Censoring was performed using the date of last known contact for those who were alive at the time of analysis.

End point type	Secondary

End point timeframe:

Approximately 10 years

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Participants				
Died (event)	125	136		
Censored, follow-up ended	313	296		
Censored, follow-up ongoing	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Distant metastasis-free survival (DMFS) events

End point title	Percentage of Participants with Distant metastasis-free survival (DMFS) events

End point description:

The first appearance of distant metastasis or all-cause mortality were used as events. Censoring was performed using the date of the last assessment for those who were alive without distant metastasis at the time of analysis.

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Participants				
Relapsed (event)	106	150		
Died (event)	4	2		
Censored, follow-up ended at Primary Completion	99	131		
Censored, follow-up ongoing at Primary Completion	229	149		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant metastasis-free survival (DMFS)

End point title	Distant metastasis-free survival (DMFS)

End point description:

Distant metastasis-free survival (DMFS) was defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurred first. The first appearance of distant metastasis or all-cause mortality were used as events. Censoring was performed using the date of the last assessment for those who were alive without distant metastasis at the time of analysis.

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Months				
median (full range (min-max))	999 (999 to 999)	999 (41.2 to 999)		

Statistical analyses

Statistical analysis title	Distant metastasis-free survival (DMFS)

Statistical analysis description:

Hazard ratio is estimated using Pike estimator.

Comparison groups	Dabrafenib and Trametinib combination therapy v Dabrafenib and Trametinib placebos
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.65

Secondary: Percentage of Participants with Freedom from relapse (FFR) events

End point title	Percentage of Participants with Freedom from relapse (FFR) events

End point description:

The first appearance of local/distant metastasis or mortality due to disease recurrence or toxicity were used as events. Censoring was performed using the date of last assessment for those who were alive without local/distant metastasis or new primary melanoma at the time of analysis. FFR was censored if patients died from causes other than melanoma or treatment-related toxicity at the date of death.

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Participants				
Relapsed (event)	163	247		
Died (event)	2	0		
Censored, follow-up ended at Primary Completion	44	36		
Censored, follow-up ongoing at Primary Completion	229	149		

Statistical analyses

No statistical analyses for this end point

Secondary: Freedom from relapse (FFR)

End point title	Freedom from relapse (FFR)

End point description:

Freedom from relapse (FFR) was defined as the interval from randomization to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment -related toxicity at the date of death. The first appearance of local/distant metastasis or mortality due to disease recurrence or toxicity were used as events. Censoring was performed using the date of last assessment for those who were alive without local/distant metastasis or new primary melanoma at the time of analysis. FFR was censored if patients died from causes other than melanoma or treatment-related toxicity at the date of death.

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Months				
median (full range (min-max))	999 (44.5 to 999)	16.6 (12.7 to 22.3)		

Statistical analyses

Statistical analysis title	Freedom from relapse (FFR)
Statistical analysis description:	
Hazard ratio is estimated using Pike estimator.	
Comparison groups	Dabrafenib and Trametinib combination therapy v Dabrafenib and Trametinib placebos
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.57

Post-hoc: All collected deaths

End point title	All collected deaths
End point description:	
Pre-treatment deaths were collected from day of participant’s informed consent to the day before first dose of study medication. On-treatment deaths were collected from first dose of study treatment to 30 days after last dose of study medication (on-treatment), up to approximately 12 months. Deaths were collected in the post treatment survival follow up from 31 days after last dose of study medication until the end of the study, up to approximately 126 months. These are not considered AEs	
End point type	Post-hoc
End point timeframe:	
Pre-treatment deaths: Up to 28 days prior to treatment. On-treatment deaths: Up to approximately 12 months. Post-treatment deaths: Up to approximately 126 months	

End point values	Dabrafenib and Trametinib combination therapy	Dabrafenib and Trametinib placebos		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	432		
Units: Participants				
Pre-treatment deaths	0	0		
On-treatment deaths	4	1		
Post-treatment deaths	121	135		
All deaths	125	136		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment to 30 days after last dose of study medication (on-treatment), up to approximately 12 months.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Dabrafenib + @Trametinib

Reporting group description:

Dabrafenib + @Trametinib

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Dabrafenib + @Trametinib	Total	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	155 / 435 (35.63%)	199 / 867 (22.95%)	44 / 432 (10.19%)
number of deaths (all causes)	4	5	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	2 / 435 (0.46%)	4 / 867 (0.46%)	2 / 432 (0.46%)
occurrences causally related to treatment / all	0 / 5	1 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acanthoma			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 435 (0.23%)	2 / 867 (0.23%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	3 / 435 (0.69%)	6 / 867 (0.69%)	3 / 432 (0.69%)
occurrences causally related to treatment / all	5 / 5	8 / 9	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland adenoma			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			

subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 435 (0.23%)	4 / 867 (0.46%)	3 / 432 (0.69%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo maligna			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	1 / 435 (0.23%)	2 / 867 (0.23%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal nodular hyperplasia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenoma			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	6 / 435 (1.38%)	6 / 867 (0.69%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	4 / 6	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular occlusion			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	3 / 435 (0.69%)	3 / 867 (0.35%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	13 / 435 (2.99%)	13 / 867 (1.50%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	18 / 18	18 / 18	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	67 / 435 (15.40%)	71 / 867 (8.19%)	4 / 432 (0.93%)
occurrences causally related to treatment / all	84 / 85	85 / 89	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular mass			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Priapism			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 435 (0.69%)	4 / 867 (0.46%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Obsessive-compulsive disorder			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 435 (0.69%)	3 / 867 (0.35%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	13 / 435 (2.99%)	18 / 867 (2.08%)	5 / 432 (1.16%)
occurrences causally related to treatment / all	14 / 14	19 / 19	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular systolic pressure increased			

subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	1 / 435 (0.23%)	2 / 867 (0.23%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Demyelinating polyneuropathy			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 435 (0.23%)	2 / 867 (0.23%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningoradiculitis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	4 / 435 (0.92%)	4 / 867 (0.46%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	4 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood loss anaemia			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central serous chorioretinopathy			
subjects affected / exposed	4 / 435 (0.92%)	4 / 867 (0.46%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	4 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinopathy			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 435 (0.92%)	4 / 867 (0.46%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	4 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic toxicity			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panniculitis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema nodosum			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian dysfunction			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess jaw			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parvovirus infection			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	3 / 435 (0.69%)	3 / 867 (0.35%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin infection			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	8 / 435 (1.84%)	9 / 867 (1.04%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 12	0 / 13	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	5 / 435 (1.15%)	6 / 867 (0.69%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	1 / 7	1 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 435 (0.92%)	4 / 867 (0.46%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinitis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pustular			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			

subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 435 (0.69%)	3 / 867 (0.35%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 435 (0.92%)	4 / 867 (0.46%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 435 (0.00%)	1 / 867 (0.12%)	1 / 432 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 867 (0.12%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 435 (0.46%)	2 / 867 (0.23%)	0 / 432 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dabrafenib + @Trametinib	Total	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	414 / 435 (95.17%)	757 / 867 (87.31%)	343 / 432 (79.40%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	64 / 435 (14.71%)	70 / 867 (8.07%)	6 / 432 (1.39%)
occurrences (all)	78	88	10
Aspartate aminotransferase increased			
subjects affected / exposed	61 / 435 (14.02%)	68 / 867 (7.84%)	7 / 432 (1.62%)
occurrences (all)	72	81	9
Blood alkaline phosphatase increased			
subjects affected / exposed	31 / 435 (7.13%)	32 / 867 (3.69%)	1 / 432 (0.23%)
occurrences (all)	35	36	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	22 / 435 (5.06%)	23 / 867 (2.65%)	1 / 432 (0.23%)
occurrences (all)	26	27	1
Vascular disorders			
Lymphoedema			
subjects affected / exposed	34 / 435 (7.82%)	58 / 867 (6.69%)	24 / 432 (5.56%)
occurrences (all)	37	65	28
Hypertension			
subjects affected / exposed	49 / 435 (11.26%)	85 / 867 (9.80%)	36 / 432 (8.33%)
occurrences (all)	57	95	38
Nervous system disorders			
Headache			
subjects affected / exposed	170 / 435 (39.08%)	272 / 867 (31.37%)	102 / 432 (23.61%)
occurrences (all)	317	494	177
Dizziness			
subjects affected / exposed	34 / 435 (7.82%)	67 / 867 (7.73%)	33 / 432 (7.64%)
occurrences (all)	45	86	41
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	34 / 435 (7.82%)	38 / 867 (4.38%)	4 / 432 (0.93%)
occurrences (all)	53	59	6
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	66 / 435 (15.17%)	95 / 867 (10.96%)	29 / 432 (6.71%)
occurrences (all)	113	150	37
Oedema peripheral			
subjects affected / exposed	58 / 435 (13.33%)	77 / 867 (8.88%)	19 / 432 (4.40%)
occurrences (all)	76	100	24
Pyrexia			
subjects affected / exposed	248 / 435 (57.01%)	293 / 867 (33.79%)	45 / 432 (10.42%)
occurrences (all)	852	914	62
Fatigue			
subjects affected / exposed	204 / 435 (46.90%)	326 / 867 (37.60%)	122 / 432 (28.24%)
occurrences (all)	298	457	159
Chills			
subjects affected / exposed	158 / 435 (36.32%)	177 / 867 (20.42%)	19 / 432 (4.40%)
occurrences (all)	384	406	22
Asthenia			
subjects affected / exposed	58 / 435 (13.33%)	100 / 867 (11.53%)	42 / 432 (9.72%)
occurrences (all)	74	120	46
Eye disorders			
Dry eye			
subjects affected / exposed	22 / 435 (5.06%)	35 / 867 (4.04%)	13 / 432 (3.01%)
occurrences (all)	23	38	15
Vision blurred			
subjects affected / exposed	27 / 435 (6.21%)	43 / 867 (4.96%)	16 / 432 (3.70%)
occurrences (all)	30	47	17
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	143 / 435 (32.87%)	208 / 867 (23.99%)	65 / 432 (15.05%)
occurrences (all)	206	310	104
Constipation			
subjects affected / exposed	51 / 435 (11.72%)	78 / 867 (9.00%)	27 / 432 (6.25%)
occurrences (all)	59	92	33
Abdominal pain upper			

subjects affected / exposed	31 / 435 (7.13%)	58 / 867 (6.69%)	27 / 432 (6.25%)
occurrences (all)	37	75	38
Abdominal pain			
subjects affected / exposed	33 / 435 (7.59%)	56 / 867 (6.46%)	23 / 432 (5.32%)
occurrences (all)	45	73	28
Vomiting			
subjects affected / exposed	120 / 435 (27.59%)	163 / 867 (18.80%)	43 / 432 (9.95%)
occurrences (all)	208	267	59
Nausea			
subjects affected / exposed	173 / 435 (39.77%)	261 / 867 (30.10%)	88 / 432 (20.37%)
occurrences (all)	284	413	129
Dyspepsia			
subjects affected / exposed	23 / 435 (5.29%)	49 / 867 (5.65%)	26 / 432 (6.02%)
occurrences (all)	25	68	43
Dry mouth			
subjects affected / exposed	41 / 435 (9.43%)	56 / 867 (6.46%)	15 / 432 (3.47%)
occurrences (all)	52	71	19
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	73 / 435 (16.78%)	106 / 867 (12.23%)	33 / 432 (7.64%)
occurrences (all)	82	121	39
Dyspnoea			
subjects affected / exposed	30 / 435 (6.90%)	47 / 867 (5.42%)	17 / 432 (3.94%)
occurrences (all)	32	51	19
Epistaxis			
subjects affected / exposed	41 / 435 (9.43%)	43 / 867 (4.96%)	2 / 432 (0.46%)
occurrences (all)	71	74	3
Oropharyngeal pain			
subjects affected / exposed	39 / 435 (8.97%)	54 / 867 (6.23%)	15 / 432 (3.47%)
occurrences (all)	52	68	16
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	24 / 435 (5.52%)	42 / 867 (4.84%)	18 / 432 (4.17%)
occurrences (all)	26	45	19
Dermatitis acneiform			

subjects affected / exposed	54 / 435 (12.41%)	64 / 867 (7.38%)	10 / 432 (2.31%)
occurrences (all)	75	86	11
Dry skin			
subjects affected / exposed	55 / 435 (12.64%)	87 / 867 (10.03%)	32 / 432 (7.41%)
occurrences (all)	67	99	32
Erythema			
subjects affected / exposed	53 / 435 (12.18%)	68 / 867 (7.84%)	15 / 432 (3.47%)
occurrences (all)	63	78	15
Hyperhidrosis			
subjects affected / exposed	30 / 435 (6.90%)	37 / 867 (4.27%)	7 / 432 (1.62%)
occurrences (all)	58	65	7
Night sweats			
subjects affected / exposed	23 / 435 (5.29%)	34 / 867 (3.92%)	11 / 432 (2.55%)
occurrences (all)	29	42	13
Rash maculo-papular			
subjects affected / exposed	31 / 435 (7.13%)	42 / 867 (4.84%)	11 / 432 (2.55%)
occurrences (all)	35	48	13
Rash			
subjects affected / exposed	112 / 435 (25.75%)	166 / 867 (19.15%)	54 / 432 (12.50%)
occurrences (all)	175	241	66
Pruritus			
subjects affected / exposed	47 / 435 (10.80%)	92 / 867 (10.61%)	45 / 432 (10.42%)
occurrences (all)	61	120	59
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	24 / 435 (5.52%)	30 / 867 (3.46%)	6 / 432 (1.39%)
occurrences (all)	27	33	6
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	70 / 435 (16.09%)	110 / 867 (12.69%)	40 / 432 (9.26%)
occurrences (all)	100	145	45
Muscle spasms			
subjects affected / exposed	40 / 435 (9.20%)	53 / 867 (6.11%)	13 / 432 (3.01%)
occurrences (all)	55	71	16
Back pain			

subjects affected / exposed	38 / 435 (8.74%)	72 / 867 (8.30%)	34 / 432 (7.87%)
occurrences (all)	45	109	64
Arthralgia			
subjects affected / exposed	122 / 435 (28.05%)	190 / 867 (21.91%)	68 / 432 (15.74%)
occurrences (all)	194	284	90
Pain in extremity			
subjects affected / exposed	60 / 435 (13.79%)	98 / 867 (11.30%)	38 / 432 (8.80%)
occurrences (all)	93	140	47
Infections and infestations			
Folliculitis			
subjects affected / exposed	24 / 435 (5.52%)	33 / 867 (3.81%)	9 / 432 (2.08%)
occurrences (all)	27	39	12
Nasopharyngitis			
subjects affected / exposed	41 / 435 (9.43%)	89 / 867 (10.27%)	48 / 432 (11.11%)
occurrences (all)	54	117	63
Urinary tract infection			
subjects affected / exposed	26 / 435 (5.98%)	34 / 867 (3.92%)	8 / 432 (1.85%)
occurrences (all)	41	50	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	47 / 435 (10.80%)	72 / 867 (8.30%)	25 / 432 (5.79%)
occurrences (all)	56	83	27

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2012	Amendment 1: • Updated RFS and OS analysis and study completion definitions; • Deleted the formal interim efficacy analysis; • Added details of randomization capping and interim analysis for OS at the time of the RFS analysis; • Updated male contraception requirements to align with current standard for dabrafenib and trametinib; • Revised Dose Modification Guidelines for Pyrexia, Visual Changes, and LVEF; • Added table showing statistical power scenario for OS analysis; • Minor changes for clarification and consistency throughout the protocol
12 November 2012	Amendment 2: • Country specific amendment for France to include tables for the management and dose modification for hypertension and renal insufficiency in response to a request from the French regulatory agency
13 December 2012	Amendment 3: • Added CT/MRI assessment at Month 21; • Included 80% power calculation for OS; • Provided the rationale for use of the Pike estimator of the treatment hazard ratio; • Updated male and female contraception requirements
17 January 2013	Amendment 4: • Country specific amendment for Sweden to include Risk/Benefit Assessment in Section 1 at the request of the Swedish regulatory agency
24 October 2013	Amendment 5: • Clarifications and updates to eligibility criteria; • Deleted exclusion for glucose-6-phosphate dehydrogenase (G6PD) deficiency; • Clarified follow-up assessments required for subjects that discontinue treatment prior to Month 12 without evidence of disease recurrence; • Updated dosing instructions; • Updated dose modification guidelines for visual changes; • Updated guidance for symptomatic decreased LVEF; • Updated guidelines for QTc prolongation; • Updated prohibited and cautionary medications; • Clarifications and updates to the Time and Events tables; • Clarified imaging requirements for efficacy assessments; • Added collection of new malignancy information; • Added Appendix 15 to address request by French Regulatory Authority for additional monitoring following discontinuation of dabrafenib (applied only to subjects enrolled in France)
05 October 2016	Amendment 6: • Deleted or replaced references to GSK or its staff with that of Novartis/Novartis and its authorized agents and administrative changes to align with Novartis processes and procedures
31 May 2017	Amendment 7: • Updated Sponsor contact information; • Added language to state the primary analysis of RFS can be performed using a data cut-off at approximately 2.5 years after Last patient First Dose. Updated data-cut-off date for final RFS analysis and provided related updated statistical assumptions; • Clarified that the primary analysis for RFS was the first interim analysis for Overall Survival and added a second interim analysis for survival after approximately 299 events
21 December 2018	Amendment 8: • Updated the Final OS analysis to occur after 50% of OS events rather than at 70% and addressed statistical considerations in the relevant sections; • Statistical assumptions updated for Statistical Power Scenarios for Overall Survival (Additional analyses added for 5-year and study completion RFS rates / Additional descriptive analysis added for post-recurrence antineoplastic treatment); • Updates made to the Time and events Schedule to reduce the number of assessments for both pre-and post-recurrence after patients have been on study for more than 60 months

05 November 2021	Amendment 9: • Ceased central imaging collection; • Disruption proof language has been added in the event of a public health emergency how the site should proceed if the subject could not attend study visits at site; • Clarification provided, PK samples for ocular events were no longer required for subjects that discontinued study treatment; • Updates made in Prompt reporting of SAEs and other events for Novartis section based on feedback from the Federal Institute for Drugs and Medical Devices (BfArM) in Germany to require prompt SAE follow up reporting
08 February 2023	Amendment 10: • Updated the Final OS analysis to occur when approximately 260 events occurred (or by the end of Jul-2023, whichever comes first); • All remaining alpha was spent for this final OS analysis by taking into account alpha spent at the first interim analysis; • Updated number of OS events and updated the percentage (%) of statistical power for 255, 260 and 299 events. Additional text regarding statistical power added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Notes: