Clinical trial results:
A Phase II, open-label study to assess the safety and efficacy of oral MEK162 in adults with locally advanced and unresectable or metastatic malignant cutaneous melanoma, harboring BRAFV600 or NRAS mutations

Summary

EudraCT number	2010-023412-13
Trial protocol	NL DE IT
Global end of trial date	06 February 2023

Results information

Result version number	v1 (current)
This version publication date	07 February 2024
First version publication date	07 February 2024

Trial information

Trial identification

Sponsor protocol code	CMEK162X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01320085
WHO universal trial number (UTN)	-
Other trial identifiers	CMEK162X2201: Other Study ID

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	30 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the objective response rates (ORRs) of MEK162 when administered orally as 45 milligram (mg) twice daily (BID), to adult subjects with advanced, unresectable cutaneous malignant melanoma, i)harboring BRAFV600 or ii) harboring NRAS mutations and iii) when administered orally as 60 mg BID, to adult subjects with advanced, unresectable cutaneous malignant melanoma, harboring BRAFV600 mutations.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 20
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Netherlands: 40
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	183
EEA total number of subjects	139

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)	120
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included only those subjects for whom the presence of a v-raf murine sarcoma viral oncogene homolog B1 (BRAFV600) or Neuroblastoma RAS viral oncogene homolog (NRAS) gene mutation in the tumor tissue was determined.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Binimetinib 45 mg BRAF

Arm description:

Subjects with BRAF mutations received an oral dose of 45 milligrams (mg) of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

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

Dosage and administration details:

Oral dose of 45 mg binimetinib twice daily

Arm title	Binimetinib 45 mg NRAS

Arm description:

Subjects with NRAS mutations received an oral dose of 45 mg of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

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

Dosage and administration details:

Oral dose of 45 mg binimetinib twice daily

Arm title	Binimetinib 60 mg BRAF

Arm description:

Subjects with BRAF mutations received an oral dose of 60 mg of binimetinib (4 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Arm type	Experimental

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

Dosage and administration details:

Oral dose of 60 mg binimetinib twice daily

Number of subjects in period 1	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF
Started	41	117	25
Completed	0	0	0
Not completed	41	117	25
Consent withdrawn by subject	2	4	1
Adverse events	12	20	5
Protocol Deviation	1	-	1
Administrative problems	-	-	1
Disease Progression	26	93	17

Baseline characteristics

Reporting groups	
Reporting group title	Binimetinib 45 mg BRAF
Reporting group description:	
Subjects with BRAF mutations received an oral dose of 45 milligrams (mg) of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.	
Reporting group title	Binimetinib 45 mg NRAS
Reporting group description:	
Subjects with NRAS mutations received an oral dose of 45 mg of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.	
Reporting group title	Binimetinib 60 mg BRAF
Reporting group description:	
Subjects with BRAF mutations received an oral dose of 60 mg of binimetinib (4 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.	

Reporting group values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF
Number of subjects	41	117	25
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)	30	67	23
From 65-84 years	11	50	2
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	53.7	59.6	51.3
standard deviation	± 14.59	± 13.74	± 9.81
Sex: Female, Male Units: Subjects			
Female	19	33	17
Male	22	84	8
Race/Ethnicity, Customized Units: Subjects			
Caucasian	41	117	25
Ethnicity Units: Subjects			
Hispanic or Latino	0	10	0
Other	41	107	25

Reporting group values	Total		
Number of subjects	183		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	120		
From 65-84 years	63		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	69		
Male	114		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	183		
Ethnicity Units: Subjects			
Hispanic or Latino	10		
Other	173		

End points

End points reporting groups

Reporting group title	Binimetinib 45 mg BRAF

Reporting group description:

Subjects with BRAF mutations received an oral dose of 45 milligrams (mg) of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	Binimetinib 45 mg NRAS

Reporting group description:

Subjects with NRAS mutations received an oral dose of 45 mg of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	Binimetinib 60 mg BRAF

Reporting group description:

Subjects with BRAF mutations received an oral dose of 60 mg of binimetinib (4 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by participant refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Primary: Percentage of Subjects With Objective Response (OR)

End point title	Percentage of Subjects With Objective Response (OR)[1]

End point description:

Objective response as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.0, was defined as subjects with a best overall response of complete response (CR) or partial response (PR), were recorded from date of randomization or date of start of treatment until date of first documentation of progressive disease (PD) or death due to any cause. CR was defined as complete disappearance of all target and non-target lesions, and sustained for at least 4 weeks apart before progression. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 millimeter (mm). PR defined as at least 30 percent (%) decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. The full analysis set included all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

From date of start of treatment until date of first documentation of PD or death due to any cause, whichever occurred first (maximum duration of up to 33 months).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Percentage of subjects				
number (confidence interval 95%)	4.9 (0.6 to 16.5)	14.5 (8.7 to 22.2)	12.0 (2.5 to 31.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS as assessed by investigator per RECIST v1.0, was defined as time (in months) from the date of start of treatment to first documentation of PD or date of death due to any cause or data censoring date, whichever occurred first. PD for target disease=at least a 20% increase in sum of longest diameters of all measured target lesions, taking as reference smallest sum on study (including baseline sum if it was smallest on study),sum also demonstrated absolute increase of greater than or equal to (>=) 5 millimeter (mm),or appearance of >=1 new lesions. For non-target disease:PD = unequivocal progression of pre-existing lesions and if overall tumor burden increased sufficiently to merit discontinuation of therapy; appearance of any new unequivocal malignant lesion was also considered PD. If a subject did not have an event, data censoring was done at date of last adequate tumor assessment. Analysis: Kaplan-Meier method. Full analysis set was used.

End point type	Secondary

End point timeframe:

From date of start of treatment until date of first documentation of PD or date of death due to any cause or date of data censoring, whichever occurred first (maximum duration of up to 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: months				
median (confidence interval 95%)	3.5 (1.9 to 3.8)	3.6 (2.6 to 3.8)	1.8 (1.5 to 3.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time (in months) from the date of start of treatment to the date of death due to any cause or data censoring date, whichever occurred first. Subjects last known to be alive were censored at date of last contact. Analysis was performed using Kaplan-Meier method. Here 99999 indicates data could not be estimated due to less number of subjects with event. The full analysis set included all subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From date of start of treatment to date of death due to any cause or date of censoring, whichever occurred first (maximum duration of up to 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	16.6 (4.9 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR as assessed by investigator according to RECIST v1.0, was defined as the time (in months) from date of start of treatment until first documented response (CR/PR) or data censoring date, whichever occurred first. CR =complete disappearance of all target and non-T lesions sustained for at least 4 weeks apart before progression. Any pathological lymph nodes (Target/Non-Target) reduced in short axis to <10 mm. PR=at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. Subjects who did not achieve a confirmed PR/CR, were censored at last adequate tumor assessment date when they did not progress (including deaths not due to underlying disease) or at maximum follow-up (from study start to study end date) when subject had an event for progression-free survival. Full analysis set was used. Number of subjects analyzed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the date of start of treatment to the first documentation of objective response (CR or PR) or data censoring date, whichever occurred first (maximum duration of up to 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	17	3	
Units: months				
median (confidence interval 95%)	2.2 (1.8 to 2.5)	1.9 (1.8 to 3.7)	1.8 (1.8 to 1.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR:time from first documentation of OR(confirmed CR/PR) to first documentation of PD/death due to any cause/data censoring date,whichever occurred first.RECIST v1.0,CR:disappearance of all target(T),Non-T lesions sustained=>4 weeks.Any pathological lymph nodes(T/non-T) reduced in short axis to <10mm. PR:>=30% decrease in sum of diameters(SOD) of T lesions,taking reference baseline SOD.PD (T lesions):at least 20% increase SOD, taking as reference smallest sum on study treatment,

absolute increase of >=5 mm/appearance of >=1 new lesions. PD (Non-T lesions)unequivocal progression of pre-existing lesions/increase in overall tumor burden leading to discontinuation of therapy/appearance of new unequivocal malignant lesion. 99999=data not estimated as less number of subjects with event. Full analysis set was evaluated. Number of subjects analyzed=subjects evaluable for endpoint.

End point type	Secondary

End point timeframe:

From first documentation of CR or PR until first documentation of tumor progression or death due to any cause or data censoring date, whichever occurred first (maximum duration of up to 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	17	3	
Units: months				
median (confidence interval 95%)	3.6 (3.6 to 3.7)	4.0 (3.7 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or 4 Treatment-Emergent Adverse Reactions Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.0

End point title	Number of Subjects With Grade 3 or 4 Treatment-Emergent Adverse Reactions Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.0

End point description:

Adverse drug reaction (ADR) was any untoward medical occurrence attributed to study drug in subjects who received study drug. As per NCI-CTCAE v4.0, Grade (G) 1: asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G2: moderate, minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily life (ADL); G3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, disabling, limiting self-care ADL; G4:life-threatening consequence, urgent intervention indicated; G5:death related to study drug. Treatment-emergent ADRs are between first dose of study drug and up to 30 days after last dose of study drug, that were absent before treatment or that worsened relative to pretreatment state. Number of subjects with any G3/4 treatment-emergent ADR were reported in this endpoint. Safety analysis set was used.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (for a maximum duration of up to 11 years, approximately)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects	19	52	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Reactions

End point title	Number of Subjects With Serious Adverse Reactions

End point description:

A serious ADR was an ADR resulting in any of the following outcomes or deemed significant for any other reason: death; life-threatening experience (immediate risk of dying); initial or prolonged inpatient hospitalization; persistent or significant disability/incapacity; congenital anomaly, important medical event. Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (for a maximum duration of up to 11 years, approximately)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects	2	12	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Grade, Version 4.0 (Hematology)

End point title	Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Grade, Version 4.0 (Hematology)

End point description:

Hematology per NCI-CTCAE included, Lymphocyte count decreased(G1:<0.8, G2:<0.8-0.5, G3:<0.5-0.2, G4:<0.2[*10^9/L]); Lymphocyte count increased(G2:>4-20, G3:>20[*10^9/L]); Neutrophil count dec(G1:<1.5, G2:<1.5-1.0, G3:<1.0-0.5, G4:<0.5[*10^9/L]); Activated partial thromboplastin(APT) time prolonged (seconds)-(G1:>1.5*ULN, G2:>1.5-2.5*ULN, G3:>2.5*ULN); Platelet count dec(G1:<75.0, G2:<75.0-50.0, G3:<50.0-25.0, G4:<25.0[*10^9/L]); Fibrinogen dec(G1:<1.0-0.75*LLN, G2:<0.75-0.5*LLN, G3:<0.5-0.25*LLN G4:<0.25*LLN); Anemia(G1:<LLN-100, G2:<100-80, G3:<80 [g/L], G4:Life-threatening, G5:death); Hemoglobin inc(G1:>0-2 g/dL above ULN, G2:>2-4 g/dL above ULN, G3:>4 g/dL above ULN); Prothrombin time (INR) inc(G1:>1-1.5, G2:>1.5-2.5,

WBC dec(G1:<3.0*10^9/L, G2:<3.0-2.0*10^9/L, G3:<2.0-1.0*10^9/L, G4:<1.0*10^9/L); WBC inc(G3:>100,000/mm3, G4:Clinical manifestations of inc in WBC, G5:death). Here:Baseline=B,Post-Baseline=PB;Segmented and Band(S&B). Safety analysis set was used.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (for a maximum duration of up to 11 years, approximately)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects				
Absolute Lymphocytes decreased: G0 B-G0 PB	28	63	10	
Absolute Lymphocytes decreased: G0 B-G1 PB	1	8	1	
Absolute Lymphocytes decreased: G0 B-G2 PB	1	7	0	
Absolute Lymphocytes decreased: G0 B-G3 PB	0	0	1	
Absolute Lymphocytes decreased: G0 B-Missing PB	1	0	1	
Absolute Lymphocytes decreased: G1 B-G0 PB	2	6	3	
Absolute Lymphocytes decreased: G1 B-G1 PB	3	12	3	
Absolute Lymphocytes decreased: G1 B-G2 PB	1	4	1	
Absolute Lymphocytes decreased: G1 B-G3 PB	1	0	0	
Absolute Lymphocytes decreased: G2 B-G0 PB	1	4	0	
Absolute Lymphocytes decreased: G2 B-G1 PB	2	2	0	
Absolute Lymphocytes decreased: G2 B-G2 PB	0	4	4	
Absolute Lymphocytes decreased: G2 B-G3 PB	0	3	1	
Absolute Lymphocytes decreased: G3 B-G2 PB	0	2	0	
Absolute Lymphocytes decreased: G3 B-G3 PB	0	1	0	
Absolute Lymphocytes decreased: Missing B-G0 PB	0	1	0	
Absolute Lymphocytes increased: G0 B to G0 PB	36	110	22	
Absolute Lymphocytes increased: G0 B to G2 PB	4	6	2	
Absolute Lymphocytes increased: G0 B to Missing PB	1	0	1	
Absolute Lymphocytes increased: Missing B to G0 PB	0	1	0	
Absolute Neutrophils (S&B): G0 B to G0 PB	38	100	21	
Absolute Neutrophils (S&B): G0 B to G1 PB	0	2	0	

Absolute Neutrophils (S&B): G0 B to G3 PB	0	0	2	
Absolute Neutrophils (S&B): G0 B to Missing PB	1	0	1	
Absolute Neutrophils (S&B): G1 B to G0 PB	0	1	0	
Absolute Neutrophils (S&B): G1 B to G1 PB	0	2	0	
Absolute Neutrophils (S&B): G1 B to G2 PB	0	1	0	
Absolute Neutrophils (S&B): G1 B to G3 PB	1	0	0	
Absolute Neutrophils (S&B): G2 B to G1 PB	0	1	0	
Absolute Neutrophils (S&B): G2 B to G3 PB	0	1	0	
Absolute Neutrophils (S&B): G3 B to G1 PB	1	0	0	
Absolute Neutrophils (S&B): G3 B to G3 PB	0	0	1	
Absolute Neutrophils (S&B): G4 B to G0 PB	0	1	0	
Absolute Neutrophils (S&B): G missing B to G0 PB	0	4	0	
Absolute Neutrophils (S&B): MissingB to MissingPB	0	4	0	
APT time: G0 B to G0 PB	31	96	19	
APT time: G0 B to G1 PB	3	14	2	
APT time: G0 B to G2 PB	0	1	1	
APT time: G0 B to G3 PB	1	0	0	
APT time: G0 B to Missing PB	1	0	1	
APT time: G1 B to G0 PB	0	1	0	
APT time: G1 B to G1 PB	1	3	1	
APT time: G1 B to G2 PB	1	1	0	
APT time: G2 B to G2 PB	0	1	0	
APT time: Missing B to G0 PB	2	0	1	
APT time: Missing B to Missing PB	1	0	0	
Platelet count (Direct): G0 B to G0 PB	36	97	21	
Platelet count (Direct): G0 B to G1 PB	2	14	3	
Platelet count (Direct): G0 B to G2 PB	0	1	0	
Platelet count (Direct): G0 B to Missing PB	1	0	1	
Platelet count (Direct): G1 B to G0 PB	1	0	0	
Platelet count (Direct): G1 B to G1 PB	0	4	0	
Platelet count (Direct): G1 B to G3 PB	0	1	0	
Platelet count (Direct): Missing B to G0 PB	1	0	0	
Fibrinogen decreased: G0 B to G0 PB	8	19	8	
Fibrinogen decreased: G0 B to G1 PB	11	52	6	
Fibrinogen decreased: G0 B to G2 PB	10	32	7	
Fibrinogen decreased: G0 B to G3 PB	0	8	2	
Fibrinogen decreased: G0 B to G4 PB	2	1	0	
Fibrinogen decreased: G0 B to Missing PB	1	0	1	
Fibrinogen decreased: G2 B to G0 PB	0	1	0	
Fibrinogen decreased: Missing B to G0 PB	6	4	1	

Fibrinogen decreased: Miising B to Missing PB	3	0	0	
Haemoglobin decreased: G0 B to G0 PB	3	22	7	
Haemoglobin decreased: G0 B to G1 PB	10	35	4	
Haemoglobin decreased: G0 B to G2 PB	1	4	1	
Haemoglobin decreased: G0 B to G3 PB	0	1	0	
Haemoglobin decreased: G0 B to Missing PB	1	0	1	
Haemoglobin decreased: G1 B to G0 PB	0	4	1	
Haemoglobin decreased: G1 B to G1 PB	16	27	6	
Haemoglobin decreased: G1 B to G2 PB	5	16	4	
Haemoglobin decreased: G1 B to G3 PB	0	3	1	
Haemoglobin decreased: G2 B to G1 PB	2	0	0	
Haemoglobin decreased: G2 B to G2 PB	3	3	0	
Haemoglobin decreased: G2 B to G3 PB	0	2	0	
Haemoglobin increased: G0 B to G0 PB	40	115	24	
Haemoglobin increased: G0 B to G1 PB	0	2	0	
Haemoglobin increased: G0 B to Missing PB	1	0	1	
Prothrombin time: G0 B to G0 PB	15	40	11	
Prothrombin time: G0 B to G1 PB	20	56	9	
Prothrombin time: G0 B to G2 PB	0	2	1	
Prothrombin time: G0 B to G3 PB	1	2	0	
Prothrombin time: G0 B to Missing PB	0	0	1	
Prothrombin time: G1 B to G1 PB	0	5	0	
Prothrombin time: G1 B to G3 PB	0	0	1	
Prothrombin time: G2 B to G2 PB	1	0	0	
Prothrombin time: G2 B to G3 PB	0	1	0	
Prothrombin time: G3 B to G3 PB	1	0	0	
Prothrombin time: Missing B to G0 PB	2	0	1	
Prothrombin time: Missing B to MissingPB	1	11	1	
WBC (Total) decreased: G0 B to G0 PB	35	93	20	
WBC (Total) decreased: G0 B to G1 PB	2	10	1	
WBC (Total) decreased: G0 B to G2 PB	0	1	0	
WBC (Total) decreased: G0 B to G3 PB	0	0	1	
WBC (Total) decreased: G0 B to Missing PB	1	0	1	
WBC (Total) decreased: G1 B to G0 PB	2	4	0	
WBC (Total) decreased: G1 B to G1 PB	0	5	0	
WBC (Total) decreased: G1 B to G2 PB	0	1	1	
WBC (Total) decreased: G2 B to G1 PB	1	2	0	
WBC (Total) decreased: G2 B to G2 PB	0	1	1	
WBC (Total) increased: G0 B to G0 PB	40	117	24	
WBC (Total) increased: G0 B to Missing PB	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Grade, Version 4.0 (Clinical Chemistry)

End point title	Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Grade, Version 4.0 (Clinical Chemistry)

End point description:

Albumin(G1:<30,G2:<30-20,G3:<20[g/L],G4:life-threatening, G5:death[D]);ALP(G1:>2.5,G2:>2.5-5.0,G3:>5.0-20.0,G4:>20.0[*ULN]);Creatine(CT) kinase(G1:>2.5,G2:>2.5-5,G3:>5-10,G4:>10[*ULN]);CT clearance (G1:<LLN-60,G2:59-30,G3:29-15,G3:<15[ml/min/1.73m^2],G5:D);CT(G1:>1.5,G2:>1.5-3.0,G3:>3.0-6.0,G4:>6.0[*ULN]);Hypomagnesemia(G1:<0.5,G2:<0.5-0.4,G3:<0.4-0.3,G4 <0.3[mmol/L],G5:D); Hypermagnesemia(G1:>1.23,G3:>1.23-3.30, G4:>3.30[mmol/L],G5:D);Hypophosphatemia Inorganic Phosphorus;IP(G1:<0.8,G2:<0.8-0.6,G3:<0.6-0.3,G4:<0.3[mmol/L], G5:D);Hypokalemia (G1:<3.0,G2:<3.0, G3:<3.0-2.5,G4:<2.5[mmol/L],G5:D);Hyperkalemia(G1:>5.5,G2:>5.5-6.0,G3:>6.0-7.0, G4:>7.0[mmol/L], G5:D);AST(G1:>3.0,G2:>3.0-5.0,G3:>5.0-20.0,G4:>20.0[*ULN]);ALT(G1:>3.0,G2:>3.0-5.0,G3:>5.0-20.0,G4:>20.0[*ULN]);Hyponatremia(G1:<130,G3:<130-120,G4 <120[mmol/L],G5:D);Hypernatremia (G1:150,G2:>150-155,G3:>155-160,G4:>160[mmol/L],G5:D);High blood bilirubin (G1:>1.5,G2:>1.5-

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (for a maximum duration of up to 11 years, approximately)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects				
Albumin: G0 B to G0 PB	14	43	11	
Albumin: G0 B to G1 PB	13	41	4	
Albumin: G0 B to G2 PB	4	19	2	
Albumin: G0 B to G3 PB	0	0	1	
Albumin: G0 B to Missing PB	1	0	1	
Albumin: G1 B to G1 PB	0	2	1	
Albumin: G1 B to G2 PB	4	3	5	
Albumin: G2 B to G0 PB	1	0	0	
Albumin: G2 B to G2 PB	1	3	0	
Albumin: G2 B to G3 PB	2	1	0	
Albumin: Missing B to G0 PB	0	3	0	
Albumin: Missing B to G1 PB	1	1	0	
Albumin: Missing B to G2 PB	0	1	0	
Alkaline phosphatase, serum: G0 B to G0 PB	0	44	0	
Alkaline phosphatase, serum: G0 B to G1 PB	0	21	0	
Alkaline phosphatase, serum: G0 B to G2 PB	0	2	0	
Alkaline phosphatase, serum: G0 B to G3 PB	0	1	0	
Alkaline phosphatase, serum: G1 B to G0 PB	0	1	0	
Alkaline phosphatase, serum: G1 B to G1 PB	0	7	0	

Alkaline phosphatase, serum: G1 B to G2 PB	0	3	0	
Alkaline phosphatase, serum: G1 B to G3 PB	0	1	0	
Alkaline phosphatase, serum: G2 B to G1 PB	0	1	0	
Alkaline phosphatase, serum: G2 B to G2 PB	0	1	0	
Alkaline phosphatase, serum: G3 B to G3 PB	0	1	0	
Alkaline phosphatase, serum: Missing B to G0 PB	0	2	3	
Alkaline phosphatase, serum: Missing B to G1 PB	0	1	1	
Alkaline phosphatase, serum: MissingB to MissingPB	41	31	21	
Creatine Kinase: G0 B to G0 PB	10	20	3	
Creatine Kinase: G0 B to G1 PB	11	34	6	
Creatine Kinase: G0 B to G2 PB	6	27	4	
Creatine Kinase: G0 B to G3 PB	4	13	6	
Creatine Kinase: G0 B to G4 PB	1	9	1	
Creatine Kinase: G0 B to Missing PB	2	0	1	
Creatine Kinase: G1 B to G3 PB	2	2	0	
Creatine Kinase: G1 B to G4 PB	1	2	0	
Creatine Kinase: G2 B to G1 PB	0	1	0	
Creatine Kinase: G2 B to G4 PB	0	1	0	
Creatine Kinase: G3 B to G4 PB	0	0	1	
Creatine Kinase: Missing B to G1 PB	2	4	0	
Creatine Kinase: Missing B to G2 PB	1	0	2	
Creatine Kinase: Missing B to G3 PB	1	3	0	
Creatine Kinase: Missing B to PB Missing	0	1	1	
Creatinine Clearance: G0 B to G0 PB	22	57	16	
Creatinine Clearance: G0 B to G1 PB	5	17	4	
Creatinine Clearance: G0 B to G2 PB	2	7	0	
Creatinine Clearance G0 B to G3 PB	0	1	1	
Creatinine Clearance: G0 B to G4 PB	0	1	0	
Creatinine Clearance G0 B to Missing PB	1	0	1	
Creatinine Clearance: G1 B to G0 PB	0	1	0	
Creatinine Clearance: G1 B to G1 PB	6	12	0	
Creatinine Clearance: G1 B to G2 PB	1	7	2	
Creatinine Clearance: G2 B to G1 PB	2	0	0	
Creatinine Clearance: G2 B to G2 PB	1	6	0	
Creatinine Clearance: G2 B to Missing PB	1	0	0	
Creatinine Clearance: Missing B to Missing PB	0	8	1	
Creatinine: G0 B to G0 PB	9	12	4	
Creatinine: G0 B to G1 PB	27	91	16	
Creatinine: G0 B to G2 PB	1	9	0	
Creatinine: G0 B to G3 PB	0	0	1	
Creatinine: G0 B to Missing PB	1	0	1	
Creatinine: G1 B to G0 PB	1	0	0	
Creatinine: G1 B to G1 PB	1	4	2	
Creatinine: G1 B to G2 PB	1	1	1	
Hypomagnesemia: G0 B to G0 PB	30	78	22	

Hypomagnesemia: G0 B to G1 PB	4	21	2	
Hypomagnesemia: G0 B to G2 PB	0	1	0	
Hypomagnesemia: G0 B to Missing PB	2	0	1	
Hypomagnesemia: G1 B to G0 PB	0	1	0	
Hypomagnesemia: G1 B to G1 PB	1	8	0	
Hypomagnesemia: G1 B to G2 PB	0	1	0	
Hypomagnesemia: Missing B to G0 PB	3	5	0	
Hypomagnesemia: Missing B to G1 PB	1	1	0	
Hypomagnesemia: Missing B to Missing PB	0	1	0	
Hypermagnesemia: G0 B to G0 PB	35	108	22	
Hypermagnesemia: G0 B to G1 PB	0	1	2	
Hypermagnesemia: G0 B to Missing PB	2	0	1	
Hypermagnesemia: G3 B to G0 PB	0	1	0	
Hypermagnesemia: Missing B to G0 PB	4	6	0	
Hypermagnesemia: Missing B to Missing PB	0	1	0	
Hypophosphatemia (IP): G0 B to G0 PB	36	79	20	
Hypophosphatemia (IP): G0 B to G1 PB	1	6	0	
Hypophosphatemia (IP): G0 B to G2 PB	0	7	0	
Hypophosphatemia (IP): G0 B to G3 PB	0	4	1	
Hypophosphatemia (IP): G0 B to Missing PB	2	0	1	
Hypophosphatemia (IP): G1 B to G0 PB	1	3	1	
Hypophosphatemia (IP): G1 B to G2 PB	0	1	0	
Hypophosphatemia (IP): G2 B to G0 PB	0	8	1	
Hypophosphatemia (IP): G2 B to G2 PB	0	7	1	
Hypophosphatemia (IP): G2 B to G3 PB	0	1	0	
Hypophosphatemia (IP): Missing B to G0 PB	1	1	0	
Hypokalemia: G0 B to G0 PB	33	93	18	
Hypokalemia: G0 B to G2 PB	3	19	6	
Hypokalemia: G0 B to G3 PB	1	0	0	
Hypokalemia: G0 B to G4 PB	1	0	0	
Hypokalemia: G0 B to Missing PB	1	0	1	
Hypokalemia: G2 B to G0 PB	1	1	0	
Hypokalemia: G2 B to G2 PB	0	3	0	
Hypokalemia: G2 B to G4 PB	1	1	0	
Hyperkalemia: G0 B to G0 PB	35	104	21	
Hyperkalemia: G0 B to G1 PB	3	6	1	
Hyperkalemia: G0 B to G2 PB	0	2	1	
Hyperkalemia: G0 B to G3 PB	0	0	1	
Hyperkalemia: G0 B to G4 PB	0	1	0	
Hyperkalemia: G0 B to Missing PB	1	0	1	
Hyperkalemia: G1 B to G0 PB	0	4	0	
Hyperkalemia: G1 B to G1 PB	1	0	0	
Hyperkalemia: G2 B to G0 PB	1	0	0	
AST: G0 B to G0 PB	11	33	5	
AST: G0 B to G1 PB	24	67	13	
AST: G0 B to G2 PB	0	5	1	
AST: G0 B to G3 PB	0	1	0	
AST: G0 B to G4 PB	0	0	1	
AST: G0 B to Missing PB	1	0	1	

AST: G1 B to G0 PB	1	0	0	
AST: G1 B to G1 PB	1	6	3	
AST: G1 B to G2 PB	2	2	0	
AST: G1 B to G3 PB	0	1	1	
AST: G2 B to G3 PB	0	1	0	
AST: G3 B to G3 PB	1	0	0	
AST: Missing B to G1 PB	0	1	0	
ALT: G0 B to G0 PB	20	58	15	
ALT: G0 B to G1 PB	17	39	5	
ALT: G0 B to G2 PB	0	5	0	
ALT: G0 B to G3 PB	0	1	0	
ALT: G0 B to G4 PB	0	0	1	
ALT: G0 B to Missing PB	1	0	1	
ALT: G1 B to G0 PB	0	1	0	
ALT: G1 B to G1 PB	3	7	2	
ALT: G1 B to G2 PB	0	4	1	
ALT: G1 B to G3 PB	0	1	0	
ALT: G2 B to G3 PB	0	1	0	
Hyponatremia: G0 B to G0 PB	25	92	17	
Hyponatremia: G0 B to G1 PB	7	11	3	
Hyponatremia: G0 B to G3 PB	1	5	0	
Hyponatremia: G0 B to Missing PB	1	0	1	
Hyponatremia: G1 B to G0 PB	3	5	2	
Hyponatremia: G1 B to G1 PB	4	2	2	
Hyponatremia: G1 B to G3 PB	0	1	0	
Hyponatremia: G3 B to G3 PB	0	1	0	
Hypernatremia: G0 B to G0 PB	37	101	24	
Hypernatremia: G0 B to G1 PB	2	14	0	
Hypernatremia: G0 B to Missing PB	1	0	1	
Hypernatremia: G1 B to G0 PB	1	2	0	
Bilirubin (total) increased: G0 B to G0 PB	36	105	22	
Bilirubin (total) increased: G0 B to G1 PB	1	7	0	
Bilirubin (total) increased: G0 B to G2 PB	0	0	1	
Bilirubin (total) increased: G0 B to G3 PB	0	2	0	
Bilirubin (total) increased: G0 B to G4 PB	0	1	0	
Bilirubin (total) increased: G0 B to Missing PB	2	0	1	
Bilirubin (total) increased: G1 B to G0 PB	1	1	1	
Bilirubin (total) increased: G1 B to G1 PB	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Vital Signs Values Based

on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Grade, Version 4.0 (Blood Pressure)

End point title	Number of Subjects With Shift From Baseline in Vital Signs Values Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Grade, Version 4.0 (Blood Pressure)

End point description:

Blood pressure included sitting diastolic blood pressure (DBP) and sitting systolic blood pressure (SBP). Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (up to maximum of 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects				
Sitting SBP (mm Hg): G0 B to G0 PB	4	6	0	
Sitting SBP (mm Hg): G0 B to G1 PB	7	14	6	
Sitting SBP (mm Hg): G0 B to G2 PB	1	8	0	
Sitting SBP (mm Hg): G0 B to G3 PB	0	2	0	
Sitting SBP (mm Hg): G1 B to G0 PB	2	1	1	
Sitting SBP (mm Hg): G1 B to G1 PB	10	29	6	
Sitting SBP (mm Hg): G1 B to G2 PB	7	23	6	
Sitting SBP (mm Hg): G1 B to G3 PB	2	10	2	
Sitting SBP (mm Hg): G0 B to Missing PB	1	0	1	
Sitting SBP (mm Hg): G2 B to G1 PB	0	4	1	
Sitting SBP (mm Hg): G2 B to G2 PB	3	8	1	
Sitting SBP (mm Hg): G2 B to G3 PB	2	5	0	
Sitting SBP (mm Hg): G2 B to Missing PB	1	0	0	
Sitting SBP (mm Hg): G3 B to G2 PB	0	3	0	
Sitting SBP (mm Hg): G3 B to G3 PB	1	4	1	
Sitting DBP (mm Hg): G0 B to G0 PB	9	14	2	
Sitting DBP (mm Hg): G0 B to G1 PB	7	23	6	
Sitting DBP (mm Hg): G0 B to G2 PB	5	8	4	
Sitting DBP (mm Hg): G0 B to G3 PB	3	6	2	
Sitting DBP (mm Hg): G0 B to Missing PB	1	0	0	
Sitting DBP (mm Hg): G1 B to G0 PB	1	1	0	
Sitting DBP (mm Hg): G1 B to G1 PB	5	19	1	
Sitting DBP (mm Hg): G1 B to G2 PB	5	17	5	
Sitting DBP (mm Hg): G1 B to G3 PB	1	10	2	
Sitting DBP (mm Hg): G1 B to Missing PB	1	0	1	
Sitting DBP (mm Hg): G2 B to G0 PB	0	1	0	
Sitting DBP (mm Hg): G2 B to G1 PB	0	3	0	
Sitting DBP (mm Hg): G2 B to G2 PB	1	9	1	
Sitting DBP (mm Hg): G2 B to G3 PB	1	4	1	

Sitting DBP (mm Hg): G3 B to G2 PB	0	1	0	
Sitting DBP (mm Hg): G3 B to G3 PB	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Markedly Abnormal Vital Sign Values: Sitting Pulse Rate

End point title	Number of Subjects With Markedly Abnormal Vital Sign Values: Sitting Pulse Rate

End point description:

Pre-defined criteria of markedly abnormal vital signs abnormalities was defined as increase or decrease from baseline (>=15 beats per minute) in pulse rate of >=120 beats per minute or less than or equal to (<=) 50 beats per minute. Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment. Here "Overall number of subjects analyzed" signifies subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (up to maximum of 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	116	24	
Units: Subjects				
Sitting pulse (High only) (beats per minute)	1	2	1	
Sitting pulse (Low only) (beats per minute)	1	6	1	
Sitting pulse (High and Low) (beats per minute)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Markedly Abnormal Vital Sign Values: Weight

End point title	Number of Subjects With Markedly Abnormal Vital Sign Values: Weight

End point description:

Vital signs included assessment of body weight. Body weight (in kilograms) measurements included high and low. Pre-defined criteria of markedly abnormal vital signs abnormalities was defined as increase or decrease from baseline in weight of >=10%. Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment. Here "number of subjects analyzed" signifies subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (up to maximum of 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	117	24	
Units: Subjects				
Weight (High)	6	11	8	
Weight (Low)	2	8	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Notable Electrocardiogram (ECG) Values

End point title	Number of Subjects With Notable Electrocardiogram (ECG) Values

End point description:

ECG findings included maximum value of >450 millisecond (msec), >480 msec and >500 msec, increase from baseline >30 msec and >60 msec for QT interval corrected using Fridericia's formula (QTcF); maximum value of >450 msec, >480 msec and >500 msec, increase from baseline >30 msec and >60 msec for QT interval corrected using Bazett's formula (QTcB); maximum value of >450 msec, >480 msec and >500 msec, increase from baseline >30 msec and >60 msec for QT interval; RR decrease >25% and to a VR >100, RR increase >25% and to a VR <50 beats per minute (bpm) for VR interval; an increase >25% and to a value >200 msec for PR interval; an increase >25% and to a value >110 msec for QRS interval. Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment. Here n= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (up to maximum of 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects				
QTcF (msec): New >450 (n=34,104,23)	5	15	3	
QTcF (msec): New >480 (n=37,109,23)	1	4	0	
QTcF(msec): New >500 (n=37,109,23)	0	0	0	
QTcF(msec):Increase from baseline>30(n=37,109,23)	4	24	5	
QTcF(msec):Increase from baseline>60(n=37,109,23)	1	1	0	
QTcB(msec): New >450 (n=30,94,21)	4	26	6	
QTcB (milsec): New >480 (n=35,108,22)	3	7	2	

QTcB (msec): New >500 (n=37,109,23)	0	3	1	
QTcB(msec):Increase from baseline>30(n=37,109,23)	6	29	6	
QTcB(msec):Increasefrom baseline >60(n=37,109,23)	0	2	3	
QT(msec): New >450 (n=37,105,23)	6	13	1	
QT(msec): New >480 (n=37,107,23)	2	4	0	
QT (msec): New >500 (n=37,109,23)	1	1	0	
QT(msec):Increase from baseline>30(n=37,109,23)	14	54	9	
QT(msec):Increase from baseline>60(n=37,109,23)	3	13	3	
VR (bpm):RR decrease>25% & to VR>100(n=37,109,23)	2	6	2	
VR (bpm):RR increase >25% & to VR<50(n=37,109,23)	3	8	2	
PR(msec):Increase>25%& to value>200(n=36,106,23)	1	6	0	
QRS(msec):Increase>25%&to value>110(n=37,109,23)	1	5	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change from Baseline in Abnormal Ophthalmoscopy Values- by Fundoscopy

End point title	Number of Subjects With Change from Baseline in Abnormal Ophthalmoscopy Values- by Fundoscopy

End point description:

Fundoscopy examination included an examination of the retina, vitreous, macula, optic nerve, optic nerve pallor, choroid and other new abnormalities in either or both eyes. New abnormalities (New Ab) were identified where the baseline assessment showed no abnormalities in a particular eye, but at the post-dose time point an abnormality was observed. New abnormalities at any time point were reported and included unscheduled assessments. Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment. Here n= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (for a maximum duration of up to 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects				
Retina: New Ab (At any time) (38,112,24)	10	43	13	
Vitreous: New Ab (At any time) (38,112,24)	2	4	1	
Macula: New Ab (At any time) (38,113,24)	7	39	9	

Optic Nerve: New Ab (At any time) (38,113,24)	1	5	1	
Optic Nerve Pallor: New Ab(At any time)(38,112,24)	0	2	0	
Choroid: New Ab(At any time) (38,112,24)	1	5	2	
Other: New Ab (At any time) (n=5,14,2)	0	6	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change from Baseline in Abnormal Ophthalmoscopy Values- by Slit Lamp Examination

End point title	Number of Subjects With Change from Baseline in Abnormal Ophthalmoscopy Values- by Slit Lamp Examination

End point description:

Slit lamp examination included an examination of the conjunctiva, cornea, iris, lens, anterior chamber, lids and other new abnormalities (New Ab) in either or both eyes. New abnormalities were identified where the baseline assessment showed no abnormalities in a particular eye, but at the post-dose time point an abnormality was observed. New abnormalities at any time point were reported and included unscheduled assessments. Safety analysis set included all subjects who had received at least one dose of study drug and had at least one valid post-baseline safety assessment. Here 99999 indicates data could not be estimated due to no subject analyzed. n=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (for a maximum duration of up to 33 months)

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	117	25	
Units: Subjects				
Conjunctiva: New Ab(At any time) (n=37,112,14)	4	25	7	
Cornea: New Ab (At any time) (n=37,112,24)	3	8	5	
Iris: New Ab (At any time) (n=37,112,24)	0	1	0	
Lens: New Ab (At any time) (n=37,112,24)	5	17	3	
Anterior chamber: New Ab(At any time)(n=36,112,24)	0	1	0	
Lids: New Ab (At any time) (n=37,112,24)	6	25	5	
Other: New abnormalities (At any time) (n=2,9,0)	1	8	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to end of Dosing Interval at Steady-State (AUCtau) of Binimetinib

End point title	Area Under the Curve From Time Zero to end of Dosing Interval at Steady-State (AUCtau) of Binimetinib

End point description:

Pharmacokinetic (PK) analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 99999 indicates data could not be estimated due to one subject analyzed. 'Number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=4,3,8)	1606.73 (± 42.55)	1704.80 (± 20.37)	1587.47 (± 42.49)	
Cycle 1, Day 15 (n=1,6,4)	2438.22 (± 99999)	2051.70 (± 32.63)	2637.48 (± 22.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Binimetinib

End point title	Maximum Plasma Concentration (Cmax) of Binimetinib

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=12,11,19)	445.8 (± 45.8)	471.6 (± 34.4)	542.5 (± 29.6)	
Cycle 1, Day 15 (n=9,13,20)	385.2 (± 50.1)	479.7 (± 41.1)	531.3 (± 44.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Binimetinib

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Binimetinib

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=12,11,19)	0.68 (0.50 to 3.25)	1.50 (0.50 to 3.00)	0.75 (0.50 to 7.98)	
Cycle 1, Day 15 (n=9,13,20)	1.50 (0.75 to 3.17)	1.48 (0.42 to 8.00)	1.42 (0.00 to 5.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Time of Last Quantifiable Concentration (AUC0-last) of Binimetinib

End point title	Area Under the Curve From Time Zero to Time of Last Quantifiable Concentration (AUC0-last) of Binimetinib

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=12,11,19)	1318.38 (± 47.38)	1447.07 (± 21.34)	1622.66 (± 37.46)	
Cycle 1, Day 15 (n=9,13,20)	1806.28 (± 40.86)	1832.06 (± 30.71)	2263.46 (± 39.84)	

Statistical analyses

No statistical analyses for this end point

Secondary: The Last Time Point of the Last Quantifiable Concentration (Tlast) of Binimetinib

End point title	The Last Time Point of the Last Quantifiable Concentration (Tlast) of Binimetinib

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=12,11,19	7.23 (3.23 to 8.00)	7.98 (7.03 to 8.05)	7.00 (3.00 to 8.28)	
Cycle 1, Day 15 (n=9,13,20)	7.50 (7.00 to 8.17)	8.00 (7.02 to 8.43)	7.50 (3.58 to 8.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Body Clearance (CL/F) of Binimetinib

End point title	Apparent Total Body Clearance (CL/F) of Binimetinib

End point description:

Drug clearance was defined as a quantitative measure of the rate at which a drug substance was removed from the plasma. Clearance obtained after oral dose was influenced by the fraction of the dose absorbed. PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 99999 indicates data could not be estimated due to one subject analyzed. 'Number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: liter/hour				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=4,3,8)	28.01 (± 46.90)	26.40 (± 20.98)	37.80 (± 30.48)	
Cycle 1, Day 15 (n=1,6,4)	18.46 (± 99999)	20.50 (± 26.73)	21.17 (± 24.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of Binimetinib

End point title	Trough Plasma Concentration (Ctrough) of Binimetinib

End point description:

Ctrough refers to plasma concentration of Binimetinib observed just before treatment administration. PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here "Overall number of subjects analyzed" signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	65	20	
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)	127.0 (± 69.6)	102.3 (± 79.1)	136.1 (± 67.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Binimetinib's Metabolite

End point title	Maximum Plasma Concentration (Cmax) of Binimetinib's Metabolite

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=12,11,19)	56.37 (± 39.22)	49.42 (± 26.49)	56.71 (± 47.62)	
Cycle 1, Day 15 (n=9,13,20)	32.31 (± 78.98)	33.55 (± 58.34)	25.47 (± 76.76)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to end of Dosing Interval at Steady-State (AUCtau) of Binimetinib's Metabolite

End point title	Area Under the Curve From Time Zero to end of Dosing Interval at Steady-State (AUCtau) of Binimetinib's Metabolite

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here, 99999 indicates data could not be estimated due to insufficient subject analyzed. 'Number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n-2,2,3)	257.73 (± 7.43)	170.11 (± 12.96)	248.82 (± 18.33)	
Cycle 1, Day 15 (n=0,1,1)	99999 (± 99999)	253.93 (± 99999)	322.21 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Binimetinib's Metabolite

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Binimetinib's Metabolite

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=12,11,19)	1.50 (0.50 to 3.25)	1.50 (0.50 to 3.00)	1.50 (0.50 to 7.98)	
Cycle 1, Day 15 (n=9,13,20)	2.50 (0.75 to 3.17)	1.50 (0.50 to 8.00)	1.50 (0.00 to 8.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Time of Last Quantifiable Concentration (AUC0-last) of Binimetinib's Metabolite

End point title	Area Under the Curve From Time Zero to Time of Last Quantifiable Concentration (AUC0-last) of Binimetinib's Metabolite

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=12,11,19)	197.29 (± 46.15)	181.60 (± 29.22)	189.37 (± 50.78)	
Cycle 1, Day 15 (n=9,13,20)	157.35 (± 63.36)	129.13 (± 62.80)	87.11 (± 79.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: The Last Time Point of the Last Quantifiable Concentration (Tlast) of Binimetinib's Metabolite

End point title	The Last Time Point of the Last Quantifiable Concentration (Tlast) of Binimetinib's Metabolite

End point description:

PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here 'number analyzed' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1.5, 3, 8 hours on Day 1 and Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	105	23	
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=12,11,19)	7.23 (3.23 to 8.00)	7.98 (7.03 to 8.05)	7.00 (3.00 to 8.28)	
Cycle 1, Day 15 (n=9,13,20)	7.50 (7.00 to 8.17)	8.00 (2.97 to 8.43)	7.25 (1.42 to 8.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Histological Score (H-score) for Phosphorylated Extracellular Signal-Regulated Kinase (pERK) From Tumor Samples of Cytoplasmic and Nuclear Cellular Compartment

End point title	Percent Change From Baseline in Histological Score (H-score) for Phosphorylated Extracellular Signal-Regulated Kinase (pERK) From Tumor Samples of Cytoplasmic and Nuclear Cellular Compartment

End point description:

Percent change from baseline in H-score for pERK from tumor samples was assessed and summarized. The H-score is a method of assessing the extent of nuclear immunoreactivity, applicable to steroid receptors. The full analysis set included all randomized subjects who received at least one dose of study drug. Here "Overall number of subjects analyzed" signifies subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to maximum duration of up to 33 months

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	8	4	
Units: Percent change				
arithmetic mean (standard deviation)				
Cytoplasmic: Percent change from baseline	-10.90 (± 26.460)	-50.11 (± 22.576)	-9.85 (± 59.566)	
Nuclear: Percent change from baseline	195.19 (± 219.585)	-66.83 (± 47.524)	-32.35 (± 83.258)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of Binimetinib's Metabolite

End point title	Trough Plasma Concentration (Ctrough) of Binimetinib's

	Metabolite

End point description:

Ctrough refers to plasma concentration of Binimetinib's metabolite observed just before treatment administration. PK analysis set included all subjects who had at least one blood sample providing evaluable PK data. Here "Overall number of subjects analyzed" signifies subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Day 15 of Cycle 1

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	65	20	
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)	12.85 (± 80.44)	11.63 (± 123.41)	16.10 (± 104.21)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Delta CT Values for Dual Specificity Phosphatase 6 (DUSP6) Expression From Tumor Samples

End point title	Percent Change From Baseline in Delta CT Values for Dual Specificity Phosphatase 6 (DUSP6) Expression From Tumor Samples

End point description:

The percentage change in DUSP6 gene expression was derived from the Relative Expression Ratio (RER) computed via the Delta Ct method. DUSP6, a protein coding gene was used as a biomarker of inhibition of the mitogen-activated protein kinase (MEK) pathway. The full analysis set included all randomized subjects who received at least one dose of study drug. Here "Overall number of subjects analyzed" signifies subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to maximum duration of up to 33 months

End point values	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	8	3	
Units: Percent change				
arithmetic mean (standard deviation)	-50.25 (± 12.069)	-30.82 (± 42.836)	29.48 (± 73.145)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 30 days after last dose (for a maximum duration of up to 11 years, approximately)

Adverse event reporting additional description:

Same event may appear as both an AE and Serious Adverse Events (SAE). However, what is presented are distinct events. An event may be categorized as serious in one participant and as non-serious in another, or a participant may have experienced both a serious and non-serious event. Analysis performed on safety set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Binimetinib 45 mg BRAF

Reporting group description:

Subjects with BRAF mutations received an oral dose of 45 milligrams (mg) of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by subjects refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	Binimetinib 45 mg NRAS

Reporting group description:

Subjects with NRAS mutations received an oral dose of 45 mg of binimetinib (3 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by subjects refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	Binimetinib 60 mg BRAF

Reporting group description:

Subjects with BRAF mutations received an oral dose of 60 mg of binimetinib (4 tablets each of 15 mg) twice daily, for each 28 days treatment cycle until development of unacceptable toxicity, disease progression, treatment discontinuation by subjects refusal or investigator's decision whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Serious adverse events	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 41 (26.83%)	39 / 117 (33.33%)	9 / 25 (36.00%)
number of deaths (all causes)	5	51	10
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Retained placenta or membranes			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 41 (2.44%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			

subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	0 / 25 (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
Laryngeal oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate irregular			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

International normalised ratio increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	0 / 25 (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
Generalised tonic-clonic seizure			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	0 / 25 (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	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Skin infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal viral infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	1 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Binimetinib 45 mg BRAF	Binimetinib 45 mg NRAS	Binimetinib 60 mg BRAF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)	117 / 117 (100.00%)	25 / 25 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blepharal papilloma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye naevus			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Fibroma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Haemangioma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Metastatic pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pyogenic granuloma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	4
Tumour pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	4
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 41 (4.88%)	25 / 117 (21.37%)	6 / 25 (24.00%)
occurrences (all)	4	49	7
Raynaud's phenomenon			

subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Erythromelalgia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	3
Haematoma			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Hyperanemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	1	2
Lymphoedema			
subjects affected / exposed	3 / 41 (7.32%)	3 / 117 (2.56%)	2 / 25 (8.00%)
occurrences (all)	3	3	5
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	12 / 41 (29.27%)	40 / 117 (34.19%)	12 / 25 (48.00%)
occurrences (all)	15	59	19
Oedema peripheral			
subjects affected / exposed	17 / 41 (41.46%)	60 / 117 (51.28%)	14 / 25 (56.00%)
occurrences (all)	28	127	25
Pyrexia			
subjects affected / exposed	5 / 41 (12.20%)	18 / 117 (15.38%)	2 / 25 (8.00%)
occurrences (all)	5	30	2
Face oedema			
subjects affected / exposed	5 / 41 (12.20%)	11 / 117 (9.40%)	5 / 25 (20.00%)
occurrences (all)	7	18	5
Asthenia			
subjects affected / exposed	2 / 41 (4.88%)	10 / 117 (8.55%)	0 / 25 (0.00%)
occurrences (all)	2	14	0
General physical health deterioration			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Axillary pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	1 / 41 (2.44%)	5 / 117 (4.27%)	2 / 25 (8.00%)
occurrences (all)	1	7	3
Facial pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Feeling cold			
subjects affected / exposed	1 / 41 (2.44%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Gait disturbance			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Granuloma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hypothermia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	2
Influenza like illness			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	2 / 25 (8.00%)
occurrences (all)	0	3	2
Localised oedema			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Malaise			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Mucosal dryness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Mucosal inflammation			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	2	1
Mucous membrane disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Non-cardiac chest pain			
subjects affected / exposed	2 / 41 (4.88%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	3	2	1
Oedema			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	2 / 25 (8.00%)
occurrences (all)	0	4	4
Pain			

subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	1	2	1
Performance status decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	2 / 41 (4.88%)	3 / 117 (2.56%)	2 / 25 (8.00%)
occurrences (all)	2	3	2
Swelling			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Xerosis			
subjects affected / exposed	1 / 41 (2.44%)	5 / 117 (4.27%)	1 / 25 (4.00%)
occurrences (all)	1	5	1
Ulcer			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Allergy to vaccine			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Penile oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Scrotal oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vaginal inflammation			

subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	11 / 117 (9.40%)	1 / 25 (4.00%)
occurrences (all)	6	13	1
Cough			
subjects affected / exposed	5 / 41 (12.20%)	5 / 117 (4.27%)	1 / 25 (4.00%)
occurrences (all)	5	5	1
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	2 / 25 (8.00%)
occurrences (all)	0	4	2
Apnoea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	1	3	0
Dyspnoea exertional			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 41 (2.44%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Nasal odour			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pharyngeal ulceration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Pulmonary oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Rhinalgia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Rhinitis allergic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Sinus disorder			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Haemoptysis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Lung disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nasal crusting			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	3
Nasal discomfort			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Painful respiration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	2 / 25 (8.00%)
occurrences (all)	0	2	3
Depression			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1

Hallucination			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	1	3	0
Mood swings			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Panic attack			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 41 (4.88%)	20 / 117 (17.09%)	2 / 25 (8.00%)
occurrences (all)	2	38	4
Alanine aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	18 / 117 (15.38%)	2 / 25 (8.00%)
occurrences (all)	1	35	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 41 (0.00%)	10 / 117 (8.55%)	3 / 25 (12.00%)
occurrences (all)	0	17	4
Ejection fraction decreased			
subjects affected / exposed	0 / 41 (0.00%)	10 / 117 (8.55%)	1 / 25 (4.00%)
occurrences (all)	0	16	1
Blood creatine phosphokinase increased			
subjects affected / exposed	12 / 41 (29.27%)	60 / 117 (51.28%)	14 / 25 (56.00%)
occurrences (all)	48	297	90
Weight decreased			

subjects affected / exposed	2 / 41 (4.88%)	8 / 117 (6.84%)	0 / 25 (0.00%)
occurrences (all)	2	11	0
Blood bilirubin increased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Amylase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Blood albumin increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
C-reactive protein increased			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	0 / 25 (0.00%)
occurrences (all)	0	7	0
Blood fibrinogen increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	2 / 25 (8.00%)
occurrences (all)	0	2	2
Blood magnesium decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	6	0
Blood phosphorus increased			

subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood potassium decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood potassium increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Blood sodium decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Blood urine present			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	0 / 41 (0.00%)	6 / 117 (5.13%)	2 / 25 (8.00%)
occurrences (all)	0	7	2
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	0	8	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	0	5	0

Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	6 / 117 (5.13%)	0 / 25 (0.00%)
occurrences (all)	0	10	0
International normalised ratio increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	4
Intraocular pressure increased			
subjects affected / exposed	1 / 41 (2.44%)	7 / 117 (5.98%)	0 / 25 (0.00%)
occurrences (all)	1	9	0
Lipase increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Prothrombin time shortened			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Sinus rhythm			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Troponin T increased			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
Weight increased			
subjects affected / exposed	3 / 41 (7.32%)	3 / 117 (2.56%)	3 / 25 (12.00%)
occurrences (all)	5	7	4
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Troponin increased			

subjects affected / exposed	2 / 41 (4.88%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	2	1	0
Injury, poisoning and procedural complications			
Anal injury			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	2	1
Injury			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Ligament injury			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Scratch			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Colour blindness			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Congenital cleft hand			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	2	2
Congenital optic nerve anomaly			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Corneal dystrophy			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	2	2
Corneal opacity congenital			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dermoid cyst			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Macular dystrophy congenital			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Cleft lip			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	3
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block first degree			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	0 / 25 (0.00%)
occurrences (all)	0	5	0
Bundle branch block right			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Defect conduction intraventricular			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	4	0

Diastolic dysfunction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hypertensive cardiomyopathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Left ventricular dysfunction			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	1	2
Sinus bradycardia			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	0 / 25 (0.00%)
occurrences (all)	0	9	0
Sinus tachycardia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Arrhythmia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Mitral valve incompetence			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dysgeusia			

subjects affected / exposed	9 / 41 (21.95%)	8 / 117 (6.84%)	1 / 25 (4.00%)
occurrences (all)	9	8	1
Headache			
subjects affected / exposed	3 / 41 (7.32%)	7 / 117 (5.98%)	4 / 25 (16.00%)
occurrences (all)	3	7	5
Dizziness			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	3 / 41 (7.32%)	6 / 117 (5.13%)	4 / 25 (16.00%)
occurrences (all)	3	6	4
Visual field defect			
subjects affected / exposed	1 / 41 (2.44%)	8 / 117 (6.84%)	1 / 25 (4.00%)
occurrences (all)	1	8	1
Disturbance in attention			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Dysaesthesia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dysarthria			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hemianopia homonymous			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Hypotonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Loss of consciousness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Migraine			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Neurological symptom			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Syncope			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	3 / 25 (12.00%)
occurrences (all)	0	3	3
Somnolence			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Memory impairment			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 41 (9.76%)	17 / 117 (14.53%)	3 / 25 (12.00%)
occurrences (all)	4	27	3
Eosinophilia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Thrombocytopenia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	5	0
Lymph node pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Lymphopenia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	3	6
Microcytic anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	6	0
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Ear swelling			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Vertigo			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	2 / 25 (8.00%)
occurrences (all)	0	3	2
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 41 (0.00%)	16 / 117 (13.68%)	1 / 25 (4.00%)
occurrences (all)	0	23	1
Blepharitis			

subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	1 / 25 (4.00%)
occurrences (all)	0	5	1
Amblyopia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Extraocular muscle paresis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blepharospasm			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	2 / 41 (4.88%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	3	3	0
Conjunctival hyperaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Conjunctival irritation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Conjunctival oedema			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis allergic			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Conjunctivochalasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Corneal disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Corneal scar			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Detachment of macular retinal			

pigment epithelium			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Detachment of retinal pigment epithelium			
subjects affected / exposed	1 / 41 (2.44%)	8 / 117 (6.84%)	0 / 25 (0.00%)
occurrences (all)	2	9	0
Diplopia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	3 / 25 (12.00%)
occurrences (all)	0	5	3
Eczema eyelids			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye allergy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Macular degeneration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye degenerative disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye discharge			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye irritation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye movement disorder			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Eye swelling			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	2	1
Eyelid disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eyelid oedema			
subjects affected / exposed	1 / 41 (2.44%)	6 / 117 (5.13%)	1 / 25 (4.00%)
occurrences (all)	1	7	1
Glaucoma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Lacrimation increased			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	1	2	1
Lenticular opacities			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Eye colour change			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Macular oedema			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	0	6	0
Posterior capsule opacification			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Meibomianitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
Ocular discomfort			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Ocular hypertension			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Ocular vascular disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Optic disc haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Optic nerve disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Orbital oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Papilloedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Paraneoplastic retinopathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Periorbital oedema			
subjects affected / exposed	3 / 41 (7.32%)	10 / 117 (8.55%)	4 / 25 (16.00%)
occurrences (all)	3	10	7
Photophobia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Maculopathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Punctate keratitis			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Retinal cyst			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Retinal detachment			
subjects affected / exposed	2 / 41 (4.88%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	3	3	0
Retinal disorder			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	3 / 25 (12.00%)
occurrences (all)	0	2	5
Retinal exudates			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Retinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Trichiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Retinal pigment epitheliopathy			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	1 / 25 (4.00%)
occurrences (all)	0	5	1
Retinal vein occlusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Retinopathy			
subjects affected / exposed	1 / 41 (2.44%)	12 / 117 (10.26%)	9 / 25 (36.00%)
occurrences (all)	1	14	11
Retinoschisis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Subretinal fluid			
subjects affected / exposed	0 / 41 (0.00%)	8 / 117 (6.84%)	1 / 25 (4.00%)
occurrences (all)	0	13	1
Retinal oedema			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vitreous disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 41 (2.44%)	7 / 117 (5.98%)	1 / 25 (4.00%)
occurrences (all)	1	8	1
Visual acuity reduced			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	2	2
Visual impairment			
subjects affected / exposed	1 / 41 (2.44%)	5 / 117 (4.27%)	0 / 25 (0.00%)
occurrences (all)	1	5	0
Vitreous detachment			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vitreous floaters			
subjects affected / exposed	2 / 41 (4.88%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	3	2	0
Ulcerative keratitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 41 (9.76%)	21 / 117 (17.95%)	10 / 25 (40.00%)
occurrences (all)	4	26	20
Nausea			
subjects affected / exposed	10 / 41 (24.39%)	37 / 117 (31.62%)	12 / 25 (48.00%)
occurrences (all)	10	39	20
Diarrhoea			
subjects affected / exposed	18 / 41 (43.90%)	57 / 117 (48.72%)	13 / 25 (52.00%)
occurrences (all)	22	78	15
Constipation			
subjects affected / exposed	3 / 41 (7.32%)	23 / 117 (19.66%)	4 / 25 (16.00%)
occurrences (all)	3	24	4

Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	13 / 117 (11.11%)	5 / 25 (20.00%)
occurrences (all)	1	14	7
Abdominal pain upper			
subjects affected / exposed	1 / 41 (2.44%)	9 / 117 (7.69%)	1 / 25 (4.00%)
occurrences (all)	1	11	1
Stomatitis			
subjects affected / exposed	1 / 41 (2.44%)	9 / 117 (7.69%)	1 / 25 (4.00%)
occurrences (all)	3	17	1
Dyspepsia			
subjects affected / exposed	1 / 41 (2.44%)	7 / 117 (5.98%)	3 / 25 (12.00%)
occurrences (all)	1	7	4
Dry mouth			
subjects affected / exposed	3 / 41 (7.32%)	5 / 117 (4.27%)	1 / 25 (4.00%)
occurrences (all)	3	5	1
Abdominal discomfort			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Anal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Anal inflammation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Aphthous ulcer			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	2 / 25 (8.00%)
occurrences (all)	1	6	3
Ascites			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	2	3	0
Cheilitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Chronic gastritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Gastric haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	4 / 25 (16.00%)
occurrences (all)	0	2	4
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Gingival bleeding			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Haematemesis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Intussusception			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1

Eructation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Faecal incontinence			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Faeces soft			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Oral discomfort			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Oral mucosal erythema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Rectal obstruction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Regurgitation			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Swollen tongue			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tongue discolouration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

Oesophagitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	15 / 41 (36.59%)	64 / 117 (54.70%)	8 / 25 (32.00%)
occurrences (all)	34	128	13
Rash			
subjects affected / exposed	16 / 41 (39.02%)	25 / 117 (21.37%)	5 / 25 (20.00%)
occurrences (all)	41	62	13
Pruritus			
subjects affected / exposed	4 / 41 (9.76%)	21 / 117 (17.95%)	3 / 25 (12.00%)
occurrences (all)	4	27	7
Dry skin			
subjects affected / exposed	1 / 41 (2.44%)	18 / 117 (15.38%)	5 / 25 (20.00%)
occurrences (all)	1	25	11
Alopecia			
subjects affected / exposed	3 / 41 (7.32%)	15 / 117 (12.82%)	2 / 25 (8.00%)
occurrences (all)	3	16	4
Erythema			
subjects affected / exposed	4 / 41 (9.76%)	8 / 117 (6.84%)	3 / 25 (12.00%)
occurrences (all)	4	8	10
Eczema			
subjects affected / exposed	3 / 41 (7.32%)	6 / 117 (5.13%)	3 / 25 (12.00%)
occurrences (all)	5	7	3
Angioedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Asteatosis			
subjects affected / exposed	2 / 41 (4.88%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	2	1	0
Milia			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Cutis laxa			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences (all)	0	4	5
Dermatitis atopic			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	1	3
Dermatitis contact			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Eczema asteatotic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Eczema weeping			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Generalised erythema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hair colour changes			
subjects affected / exposed	1 / 41 (2.44%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Hair growth abnormal			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Hair texture abnormal			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hyperkeratosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Intertrigo			

subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Keloid scar			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Chronic pigmented purpura			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Rash maculovesicular			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nail ridging			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pain of skin			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	1	4
Petechiae			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Pigmentation disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	2
Pruritus generalised			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	1	1	0

Rash erythematous			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Rash follicular			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Rash generalised			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	6	0
Rash macular			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 41 (2.44%)	7 / 117 (5.98%)	1 / 25 (4.00%)
occurrences (all)	3	13	2
Nail disorder			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
Rash papular			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	5	0
Toxic skin eruption			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Scab			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Skin discolouration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	4
Skin erosion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

Skin exfoliation			
subjects affected / exposed	2 / 41 (4.88%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Skin fissures			
subjects affected / exposed	0 / 41 (0.00%)	7 / 117 (5.98%)	2 / 25 (8.00%)
occurrences (all)	0	8	13
Skin hypopigmentation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Skin maceration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Skin plaque			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Solar dermatitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Stasis dermatitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Rosacea			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Haematuria			

subjects affected / exposed	1 / 41 (2.44%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	1	14	0
Incontinence			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Renal colic			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Renal failure			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Renal pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Obstructive uropathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)	9 / 117 (7.69%)	7 / 25 (28.00%)
occurrences (all)	3	10	8
Pain in extremity			

subjects affected / exposed	3 / 41 (7.32%)	14 / 117 (11.97%)	2 / 25 (8.00%)
occurrences (all)	3	14	2
Myalgia			
subjects affected / exposed	2 / 41 (4.88%)	13 / 117 (11.11%)	4 / 25 (16.00%)
occurrences (all)	2	26	7
Joint range of motion decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	5 / 117 (4.27%)	2 / 25 (8.00%)
occurrences (all)	1	5	5
Bone swelling			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Bursitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Flank pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	0	1	2
Groin pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Muscle fatigue			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Lupus-like syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 41 (2.44%)	8 / 117 (6.84%)	0 / 25 (0.00%)
occurrences (all)	1	9	0
Musculoskeletal pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Musculoskeletal stiffness			

subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Pain in jaw			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Sjogren's syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Trigger finger			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Limb discomfort			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	0 / 25 (0.00%)
occurrences (all)	0	5	0
Arthropathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Infections and infestations			
Rash pustular			
subjects affected / exposed	0 / 41 (0.00%)	11 / 117 (9.40%)	2 / 25 (8.00%)
occurrences (all)	0	14	6
Body tinea			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0

Cystitis			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	1 / 25 (4.00%)
occurrences (all)	0	5	1
Angular cheilitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Bronchitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Candida infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 117 (1.71%)	2 / 25 (8.00%)
occurrences (all)	1	4	3
Clostridium difficile colitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 41 (0.00%)	4 / 117 (3.42%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Corona virus infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Bacteraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Escherichia infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Erysipelas			
subjects affected / exposed	1 / 41 (2.44%)	4 / 117 (3.42%)	2 / 25 (8.00%)
occurrences (all)	1	6	2
Infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	3 / 25 (12.00%)
occurrences (all)	0	1	3
Orchitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Oral candidiasis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	2	1
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)	5 / 117 (4.27%)	0 / 25 (0.00%)
occurrences (all)	0	16	0
Lymphangitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Lip infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 41 (2.44%)	5 / 117 (4.27%)	0 / 25 (0.00%)
occurrences (all)	1	6	0
Paronychia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences (all)	1	5	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences (all)	1	3	1
Post procedural infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pulpitis dental			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Viral infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	3 / 117 (2.56%)	2 / 25 (8.00%)
occurrences (all)	2	3	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	1 / 25 (4.00%)
occurrences (all)	0	2	1

Staphylococcal bacteraemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Soft tissue infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	2 / 25 (8.00%)
occurrences (all)	0	4	15
Sinusitis			
subjects affected / exposed	0 / 41 (0.00%)	3 / 117 (2.56%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Pharyngitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Wound infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Staphylococcal skin infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Fungal skin infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 117 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 41 (12.20%)	19 / 117 (16.24%)	3 / 25 (12.00%)
occurrences (all)	6	23	4
Dehydration			

subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	2 / 25 (8.00%)
occurrences (all)	1	1	4
Hyperglycaemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	1	1	3
Hyperphosphataemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 117 (1.71%)	2 / 25 (8.00%)
occurrences (all)	0	2	2
Hypokalaemia			
subjects affected / exposed	3 / 41 (7.32%)	4 / 117 (3.42%)	1 / 25 (4.00%)
occurrences (all)	4	9	1
Hypomagnesaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 41 (0.00%)	1 / 117 (0.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Hyperkalaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 117 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported