Clinical trial results:
Phase II biomarker study evaluating the upfront combination of BRAF inhibitor dabrafenib with MEK inhibitor trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in patients with metastatic and unresectable stage III or IV melanoma harbouring an activating BRAF mutation

Summary

EudraCT number	2012-004577-12
Trial protocol	ES
Global end of trial date	19 January 2017
Results information	
Result version number	v3 (current)
This version publication date	10 October 2018
First version publication date	27 January 2018
Version creation reason	

Trial information

Trial identification	
Sponsor protocol code	116613
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	23 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate biomarkers linked to treatment response, resistance and toxicity including skin toxicity when dabrafenib and trametinib combination is given upfront or as monotherapy before the combination treatment.

Protection of trial subjects:

At the time the study was early terminated, subjects who were still receiving clinical benefit and based on the discretion of the Investigator had the option to continue treatment through Sponsor established programs in the local country

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2013
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	France: 37
Country: Number of subjects enrolled	Spain: 11
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	33
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This is an open label, randomized, phase II study to compare the combination of dabrafenib with trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in metastatic and unresectable stage III or IV melanoma. The study was terminated early due to slow enrollment and limited numbers of viable tissue samples.

Pre-assignment

Screening details:

This study was planned to enroll 54 participants randomized in 1:1:1 ratio into the three treatment arms; dabrafenib followed by combination therapy, trametinib followed by combination therapy and only combination therapy. The study was early terminated with 48 participants enrolled.

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	Dabrafenib followed by combination therapy

Arm description:

Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib was given as an oral capsule with a dose of 150 mg twice a day (BID).

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

Dosage and administration details:

Trametinib was given as an oral film-coated tablet with a dose of 2 milligrams (mg) once daily.

Arm title	Trametinib followed by combination therapy

Arm description:

Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

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

Dosage and administration details: Trametinib was given as an oral film-coated tablet with a dose of 2 milligrams (mg) once daily.	
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: Dabrafenib was given as an oral capsule with a dose of 150 mg twice a day (BID).	
Arm title	Combination therapy
Arm description: Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.	
Arm type	Experimental
Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Trametinib was given as an oral film-coated tablet with a dose of 2 milligrams (mg) once daily.	
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: Dabrafenib was given as an oral capsule with a dose of 150 mg twice a day (BID).	

Number of subjects in period 1	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy
Started	16	16	16
Completed	8	6	7
Not completed	8	10	9
Physician decision	2	1	-
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	-	6	4
Other (Study Closed/Terminated)	5	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Dabrafenib followed by combination therapy
Reporting group description:	
Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.	
Reporting group title	Trametinib followed by combination therapy
Reporting group description:	
Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.	
Reporting group title	Combination therapy
Reporting group description:	
Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.	

Reporting group values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy
Number of subjects	16	16	16
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	56.6	56.5	58.9
standard deviation	± 16.43	± 11.77	± 13.55
Gender categorical Units: Subjects			
Female	7	8	6
Male	9	8	10
Race/Ethnicity, Customized Units: Subjects			
Asian-South East Asian Heritage	0	1	0
White - White/Caucasian/European	16	15	16

Reporting group values	Total		
Number of subjects	48		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			

Female	21		
Male	27		

Race/Ethnicity, Customized Units: Subjects			
Asian-South East Asian Heritage	1		
White - White/Caucasian/European	47		

End points

End points reporting groups

Reporting group title	Dabrafenib followed by combination therapy
Reporting group description:	
Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.	
Reporting group title	Trametinib followed by combination therapy
Reporting group description:	
Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.	
Reporting group title	Combination therapy
Reporting group description:	
Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.	

Primary: Number of participants with percentage change from Baseline in extracellular signal-regulated kinase (ERK) phosphorylation (p-ERK) H score from Week 0 to Week 2

End point title	Number of participants with percentage change from Baseline in extracellular signal-regulated kinase (ERK) phosphorylation (p-ERK) H score from Week 0 to Week 2[1][2]

End point description:

Intra-tumoral expression levels of ERK measured using immunohistochemistry methods. The H score value ranged from 0 to a maximum score of 300 (strongest expression) was derived by summing the percentages of cells staining at each intensity multiplied by the weighted intensity of staining (0 [no staining], 1+ [weak staining], 2+ [medium staining] and 3+ [strongest staining]). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Percentage change from Baseline was calculated by dividing change from Baseline value by Baseline value and multiplied by 100. The data has been presented for combination therapy calculated from Week 0 to Week 2. The analysis was based on the biomarker Population which included all participants with biopsy performed at screening and at least once during treatment. Only those participants with data available at specific time point were analyzed.

End point type	Primary

End point timeframe:

Baseline (Week 0) and up to 2 weeks

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: There are no statistical data to report.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Combination therapy			
Subject group type	Reporting group			
Number of subjects analysed	5[3]			
Units: Participants				
Any Increase or No Changes	2			
Any Decrease up to 80 percent	1			
Any Decrease > 80 percent	2			

Notes:

[3] - Biomarker Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with percentage change in p-ERK H score from Week 8 to Week 10

End point title	Number of participants with percentage change in p-ERK H score from Week 8 to Week 10[4][5]

End point description:

Intra-tumoral expression levels of ERK were measured using immunohistochemistry methods. The H score value ranged from 0 to a maximum score of 300 (strongest expression) was derived by summing the percentages of cells staining at each intensity multiplied by the weighted intensity of staining (0 [no staining], 1+ [weak staining], 2+ [medium staining] and 3+ [strongest staining]). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Percentage change from Baseline was calculated by dividing change from Baseline value by Baseline value and multiplied by 100. The data has been presented for dabrafenib followed by combination therapy and trametinib followed by combination therapy, calculated from Week 8 to Week 10. Only those participants with data available at specific time point were analyzed.

End point type	Primary

End point timeframe:

Week 8 and up to 10 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[6]	3[7]		
Units: Participants				
Any Increase or No Changes	1	1		
Any Decrease up to 80 percent	0	1		
Any Decrease > 80 percent	0	1		

Notes:

[6] - Biomarker Population

[7] - Biomarker Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with overall response rate (ORR)

End point title	Number of participants with overall response rate (ORR)

End point description:

Clinical response was evaluated by ORR, which was defined as the number of participants with a confirmed or an unconfirmed complete response (CR) or partial response (PR) at any time per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR was defined as disappearance of all target lesions. PR was defined as at least a 30 percent decrease in the sum of the diameters of target lesions. Number of participants with ORR (CR+PR) has been presented. The analysis was based on the Intent-to-Treat Population (ITT) which included all the randomized participants whether or not randomized treatment was administered.

End point type	Secondary

End point timeframe:

Up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[8]	16[9]	16[10]	
Units: Participants				
Participants	11	13	11	

Notes:

[8] - Intent-to-Treat Population (ITT)

[9] - Intent-to-Treat Population (ITT)

[10] - Intent-to-Treat Population (ITT)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The odds ratio for dabrafenib followed by combination therapy versus combination therapy has been presented.

Comparison groups	Combination therapy v Dabrafenib followed by combination therapy
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.224
upper limit	4.459

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The odds ratio for trametinib followed by combination therapy versus combination therapy has been presented.

Comparison groups	Combination therapy v Trametinib followed by combination therapy
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4216
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.382
upper limit	10.166

Secondary: Number of participants with change in vital signs from Baseline

End point title	Number of participants with change in vital signs from Baseline

End point description:

Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP) and heat rate (HR) were measured. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus the Baseline value. The number of participants with heart rate "decrease to < 60" and "increase to >100" have been presented. For SBP and DBP, "any grade increase" have been presented. Any grade increase in SBP, including grade 0 (<120), grade 1 (120-139), grade 2 (140-159), grade 3 (>=160) and DBP including grade 0 (<80), grade 1 (80-89), grade 2 (90-99), grade 3 (>=100) have been presented. The analysis was based on the Safety Population which included all participants who received at least one dose of randomized treatment and was based on the actual treatment received. Only those participants available at specified time point were analyzed (represented by n=x in category titles).

End point type	Secondary

End point timeframe:

Baseline and up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[11]	16[12]	16[13]	
Units: Participants				
HR; Week 4; Decrease to <60; n=15,16,16	1	3	3	
HR; Week 4; Increase to >100; n=15,16,16	1	0	0	
HR; Week 8; Decrease to <60; n=16,16,14	1	2	2	
HR; Week 8; Increase to >100; n=16,16,14	2	0	0	
HR; Week 12; Decrease to <60; n=16,16,13	2	1	2	
HR; Week 12; Increase to >100; n=16,16,13	0	0	0	

HR; Week 16; Decrease to <60; n=14,16,13	0	0	2	
HR; Week 16; Increase to >100; n=14,16,13	0	0	0	
HR; Week 20; Decrease to <60; n=11,15,13	0	1	1	
HR; Week 20; Increase to >100; n=11,15,13	1	1	0	
HR; Week 24; Decrease to <60; n=12,14,13	1	2	2	
HR; Week 24; Increase to >100; n=12,14,13	1	2	0	
HR; Week 28; Decrease to <60; n=8,12,7	2	2	2	
HR; Week 28; Increase to >100; n=8,12,7	1	0	0	
HR; Week 32; Decrease to <60; n=7,11,8	1	0	0	
HR; Week 32; Increase to >100; n=7,11,8	1	0	0	
HR; Week 36; Decrease to <60; n=5,11,8	2	0	1	
HR; Week 36; Increase to >100; n=5,11,8	0	0	1	
HR; Week 40; Decrease to <60; n=6,11,7	1	1	0	
HR; Week 40; Increase to >100; n=6,11,7	0	0	0	
HR; Week 44; Decrease to <60; n=5,5,4	1	0	0	
HR; Week 44; Increase to >100; n=5,5,4	1	0	1	
HR; Week 48; Decrease to <60; n=5,4,4	1	0	1	
HR; Week 48; Increase to >100; n=5,4,4	0	0	1	
HR; Week 52; Decrease to <60; n=4,3,4	0	0	0	
HR; Week 52; Increase to >100; n=4,3,4	0	0	1	
HR; Week 56; Decrease to <60; n=4,3,4	1	0	3	
HR; Week 56; Increase to >100; n=4,3,4	0	0	0	
HR; Week 60; Decrease to <60; n=3,3,4	1	1	1	
HR; Week 60; Increase to >100; n=3,3,4	0	0	0	
HR; Week 64; Decrease to <60; n=3,3,3	1	0	0	
HR; Week 64; Increase to >100; n=3,3,3	0	0	0	
HR; Week 68; Decrease to <60; n=4,2,2	1	0	2	
HR; Week 68; Increase to >100; n=4,2,2	0	0	0	
HR; Week 72; Decrease to <60; n=3,2,2	0	0	0	
HR; Week 72; Increase to >100; n=3,2,2	0	0	0	
HR; Week 76; Decrease to <60; n=4,1,2	1	0	0	

HR; Week 76; Increase to >100; n=4,1,2	0	0	1	
HR; Week 80; Decrease to <60; n=3,1,2	1	0	0	
HR; Week 80; Increase to >100; n=3,1,2	0	0	0	
HR; Week 84; Decrease to <60; n=3,1,1	0	0	0	
HR; Week 84; Increase to >100; n=3,1,1	0	0	0	
HR; Week 88; Decrease to <60; n=3,1,1	1	0	0	
HR; Week 88; Increase to >100; n=3,1,1	0	0	0	
HR; Week 92; Decrease to <60; n=3,1,1	1	0	0	
HR; Week 92; Increase to >100; n=3,1,1	0	0	0	
HR; Week 96; Decrease to <60; n=3,1,1	1	0	0	
HR; Week 96; Increase to >100; n=3,1,1	0	0	0	
HR; Week 100; Decrease to <60; n=3,1,1	0	0	0	
HR; Week 100; Increase to >100; n=3,1,1	0	0	0	
HR; Week 104; Decrease to <60; n=3,1,1	0	0	0	
HR; Week 104; Increase to >100; n=3,1,1	0	0	0	
HR; Week 108; Decrease to <60; n=2,0,1	1	99999	0	
HR; Week 108; Increase to >100; n=2,0,1	0	99999	0	
HR; Week 112; Decrease to <60; n=2,0,0	1	99999	99999	
HR; Week 112; Increase to >100; n=2, 0,0	0	99999	99999	
HR; Week 116; Decrease to <60; n=1, 0,0	0	99999	99999	
HR; Week 116; Increase to >100; n=1, 0,0	0	99999	99999	
HR; Week 120; Decrease to <60; n=1, 0,0	0	99999	99999	
HR; Week 120; Increase to >100; n=1, 0,0	0	99999	99999	
HR; Week 124; Decrease to <60; n=1, 0,0	0	99999	99999	
HR; Week 124; Increase to >100; n=1, 0,0	0	99999	99999	
SBP; Week 4; Any grade increase; n=15,16,16	1	8	4	
SBP; Week 8; Any grade increase; n=16,16,14	3	5	4	
SBP; Week 12; Any grade increase; n=16,16,13	3	5	2	
SBP; Week 16; Any grade increase; n=14,16,13	4	3	2	
SBP; Week 20; Any grade increase; n=11,15, 13	2	3	1	
SBP; Week 24; Any grade increase; n=12, 14,13	2	3	2	

SBP; Week 28; Any grade increase; n=8, 12,7	2	0	0	
SBP; Week 32; Any grade increase; n=7,11, 8	2	3	2	
SBP; Week 36; Any grade increase; n=5, 11, 8	3	3	1	
SBP; Week 40; Any grade increase; n=6,11, 7	1	4	2	
SBP; Week 44; Any grade increase; n=5, 5, 4	2	0	0	
SBP; Week 48; Any grade increase; n=5,4, 4	1	1	0	
SBP; Week 52; Any grade increase; n=4,3, 4	1	0	0	
SBP; Week 56; Any grade increase; n=4, 3, 4	0	0	0	
SBP; Week 60; Any grade increase; n=3, 2, 4	1	1	0	
SBP; Week 64; Any grade increase; n=3, 3, 3	1	0	0	
SBP; Week 68; Any grade increase; n=4,2, 2	2	0	0	
SBP; Week 72; Any grade increase; n=3,2, 2	1	0	0	
SBP; Week 76; Any grade increase; n=4, 1, 2	2	0	0	
SBP; Week 80; Any grade increase; n=3, 1, 2	2	0	0	
SBP; Week 84; Any grade increase; n=3, 1,1	2	0	0	
SBP; Week 88; Any grade increase; n=3, 1,1	0	0	0	
SBP; Week 92; Any grade increase; n=3, 1, 1	2	0	0	
SBP; Week 96; Any grade increase; n=3,1, 1	2	1	0	
SBP; Week 100; Any grade increase; n=3, 1, 1	0	0	0	
SBP; Week 104; Any grade increase; n=3, 1, 1	1	0	0	
SBP; Week 108; Any grade increase; n=2,0, 1	1	99999	0	
SBP; Week 112; Any grade increase; n=2, 0, 0	0	99999	99999	
SBP; Week 116; Any grade increase; n=1, 0, 0	0	99999	99999	
SBP; Week 120; Any grade increase; n=1, 0, 0	0	99999	99999	
SBP; Week 124; Any grade increase; n=1, 0, 0	0	99999	99999	
DBP; Week 4; Any grade increase; n=15, 16, 16	2	10	5	
DBP; Week 8; Any grade increase; n=16, 16,14	4	8	3	
DBP; Week 12; Any grade increase; n=16, 16, 13	4	4	2	
DBP; Week 16; Any grade increase; n=14, 16,13	5	5	3	
DBP; Week 20; Any grade increase; n=11, 15,13	4	5	2	
DBP; Week 24; Any grade increase; n=12, 14,13	3	3	1	

DBP; Week 28; Any grade increase; n=8, 12,7	1	2	0	
DBP; Week 32; Any grade increase; n=7, 11,8	2	3	1	
DBP; Week 36; Any grade increase; n=5, 11,8	2	1	2	
DBP; Week 40; Any grade increase; n=6, 11,7	1	1	1	
DBP; Week 44; Any grade increase; n=5, 5,4	4	1	2	
DBP; Week 48; Any grade increase; n=5, 4,4	2	1	2	
DBP; Week 52; Any grade increase; n=4,3,4	2	0	0	
DBP; Week 56; Any grade increase; n=4,3,4	1	1	0	
DBP; Week 60; Any grade increase; n=3,2,4	2	0	0	
DBP; Week 64; Any grade increase; n=3,3, 3	1	0	1	
DBP; Week 68; Any grade increase; n=4,2, 2	2	0	1	
DBP; Week 72; Any grade increase; n=3,2,2	1	0	1	
DBP; Week 76; Any grade increase; n=4,1,2	2	0	1	
DBP; Week 80; Any grade increase; n=3,1,2	1	0	1	
DBP; Week 84; Any grade increase; n=3,1,1	1	0	0	
DBP; Week 88; Any grade increase; n=3,1,1	1	0	0	
DBP; Week 92; Any grade increase; n=3, 1,1	1	0	1	
DBP; Week 96; Any grade increase; n=3, 1,1	2	0	1	
DBP; Week 100; Any grade increase; n=3,1,1	1	0	0	
DBP; Week 104; Any grade increase; n=3,1,1	1	0	1	
DBP; Week 108; Any grade increase; n=2,0,1	1	99999	0	
DBP; Week 112; Any grade increase; n=2,0,0	0	99999	99999	
DBP; Week 116; Any grade increase; n=1,0,0	0	99999	99999	
DBP; Week 120; Any grade increase; n=1,0,0	0	99999	99999	
DBP; Week 124; Any grade increase; n=1,0,0	0	99999	99999	

Notes:

[11] - Safety Population

[12] - Safety Population

[13] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically significant abnormal findings

undergoing physical examinations

End point title	Number of participants with clinically significant abnormal findings undergoing physical examinations

End point description:

Complete physical examination included assessments of eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease, and of the head, neck, ears, nose, mouth, throat, thyroid, lymph nodes, extremities, and a full skin exam to assess cutaneous malignancies and proliferative skin diseases. This analysis was planned but data was not captured in the database. Abnormal changes were captured as adverse events if they were clinically significant.

End point type	Secondary

End point timeframe:

Up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: Participants				
Participants				

Notes:

[14] - Safety Population. This analysis was planned but data was not captured in the database.

[15] - Safety Population. This analysis was planned but data was not captured in the database.

[16] - Safety Population. This analysis was planned but data was not captured in the database.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change in eastern cooperative oncology group (ECOG) performance status scores from Baseline

End point title	Number of participants with change in eastern cooperative oncology group (ECOG) performance status scores from Baseline

End point description:

The ECOG scale of performance status describes the level of functioning of participants in terms of their ability to care for themselves, daily activity, and physical ability. The ECOG performance was recorded as per ECOG performance status grades ranging from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (dead). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The Baseline performance status of participants with respect to worst-case on-therapy performance status has been presented.

End point type	Secondary

End point timeframe:

Baseline and up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[17]	16[18]	16[19]	
Units: Participants				
0 to 0	5	5	6	
0 to 1	0	0	1	
0 to 2	0	0	0	
0 to 3	0	0	0	
0 to 4-5	0	0	0	
1 to 0	6	10	5	
1 to 1	3	1	2	
1 to 2	0	0	0	
1 to 3	0	0	0	
1 to 4-5	0	0	0	
2 to 0	0	0	0	
2 to 1	2	0	2	
2 to 2	0	0	0	
2 to 3	0	0	0	
2 to 4-5	0	0	0	
3 to 0	0	0	0	
3 to 1	0	0	0	
3 to 2	0	0	0	
3 to 3	0	0	0	
3 to 4-5	0	0	0	
4-5 to 0	0	0	0	
4-5 to 1	0	0	0	
4-5 to 2	0	0	0	
4-5 to 3	0	0	0	
4-5 to 4-5	0	0	0	

Notes:

[17] - Safety Population

[18] - Safety Population

[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal electrocardiograms (ECG) findings

End point title	Number of participants with abnormal electrocardiograms (ECG) findings

End point description:

Single measurements of 12-lead ECGs were obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, corrected QT interval (QTc), Bazett's Corrected QT interval (QTcB), Friderica's Corrected QT interval (QTcF). Number of participants with abnormal ECG findings (Abnormal - Not Clinically Significant and Abnormal - Clinically Significant) at any time post-Baseline visit have been presented.

End point type	Secondary

End point timeframe:

Up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[20]	16[21]	16[22]	
Units: Participants				
Abnormal - Not Clinically Significant	9	10	9	
Abnormal - Clinically Significant	0	1	0	

Notes:

[20] - Safety Population

[21] - Safety Population

[22] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with absolute change in left ventricular ejection fraction from Baseline

End point title	Number of participants with absolute change in left ventricular ejection fraction from Baseline

End point description:

Echocardiograms (ECHO) was performed to assess cardiac ejection fraction and cardiac valve morphology. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The worst-case on-therapy value has been presented.

End point type	Secondary

End point timeframe:

Baseline and up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[23]	16[24]	16[25]	
Units: Participants				
No Change Or Any Increase	11	14	11	
>0-<10 Decrease	4	2	3	
>=10 Decrease And >= Lower limit of Normal (Lln)	1	0	2	

Notes:

[23] - Safety Population

[24] - Safety Population

[25] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change in clinical chemistry parameters from Baseline

End point title	Number of participants with change in clinical chemistry parameters from Baseline

End point description:

Blood samples were collected for evaluation of clinical chemistry parameters including sodium, potassium, calcium, albumin, total protein, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GCT), phosphate, C-reactive protein (CRP), hypercalcemia, hyperkalemia, hypernatremia, hypocalcemia, hypokalemia, hyponatremia, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin and estimated creatinine clearance (CRTCE). Baseline was defined as the most recent non-missing value from a central laboratory prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The worst-case on therapy value for number of participants with any grade increase in clinical chemistry parameters for has been presented. Only those participants available at specified time point were analyzed (represented by n=x in category titles).

End point type	Secondary

End point timeframe:

Baseline and up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[26]	16[27]	16[28]	
Units: Participants				
ALT; n=16,16,16	3	13	9	
Albumin; n=16,16,16	2	5	2	
Alkaline phosphatase; n=16,16,16	5	10	4	
AST; n=16,16,16	8	15	12	
Bilirubin; n=16,16,16	0	2	0	
CRP;n=12,12,13	0	0	0	
Creatinine; n=16,16,16	0	0	0	
Direct bilirubin; n=4,6,3	0	0	0	
GCT; n=16,16,16	6	12	5	
Hypercalcemia; n=16,16,16	0	0	0	
Hyperkalemia; n=16,16,16	1	4	0	
Hypernatremia; n=16,16,16	3	4	1	
Hypocalcemia; n=16,16,16	7	7	4	
Hypokalemia; n=16,16,16	1	4	3	
Hyponatremia; n=16,16,16	7	7	5	
LDH; 16,16,15	0	0	0	
Phosphate; n=16,16,16	10	6	4	
Protein; n=16,16,16	0	0	0	
Urea; n=15,15,16	0	0	0	
CRTCE; n=5,2,5	0	0	0	

Notes:

[26] - Safety Population

[27] - Safety Population

[28] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change in hematology parameters from Baseline

End point title	Number of participants with change in hematology parameters from Baseline

End point description:

Blood samples were collected for evaluation of hematology parameters including hemoglobin, white blood cell (WBC), platelet count, basophils, eosinophils, lymphocytes, monocytes, total neutrophils, lymphocytopenia and lymphocytosis. Baseline was defined as the most recent non-missing value from a central laboratory prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The worst-case on therapy value for number of participants with any grade increase in hematology parameters for has been presented.

End point type	Secondary

End point timeframe:

Baseline and up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[29]	16[30]	16[31]	
Units: Participants				
Basophils	0	0	0	
Eosinophils	0	0	0	
Hemoglobin	4	6	4	
Leukocytes	5	9	10	
Monocytes	0	0	0	
Neutrophils	6	9	9	
Platelets	2	5	3	
Lymphocytopenia	8	6	6	
Lymphocytosis	2	0	0	

Notes:

[29] - Safety Population

[30] - Safety Population

[31] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with incidence of squamous cell carcinoma and

keratoacanthoma

End point title	Number of participants with incidence of squamous cell carcinoma and keratoacanthoma

End point description:

The safety profile of dabrafenib and trametinib in monotherapy as well as in combination therapy was characterized by determining the number of participants with incidence of squamous cell carcinoma and keratoacanthoma.

End point type	Secondary

End point timeframe:

Up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[32]	16[33]	16[34]	
Units: Participants				
Participants	1	0	0	

Notes:

[32] - Safety Population

[33] - Safety Population

[34] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with on-treatment serious adverse events (SAEs) and non-SAEs

End point title	Number of participants with on-treatment serious adverse events (SAEs) and non-SAEs

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAE is defined as any untoward medical occurrence that, at any dose results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability, is a congenital anomaly/ birth defect, other situations and is associated with liver injury or impaired liver function.

End point type	Secondary

End point timeframe:

Up to 3.2 years

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[35]	16[36]	16[37]	
Units: Participants				
Any Non-SAE	16	16	15	

Any SAE	8	7	4	

Notes:

[35] - Safety Population

[36] - Safety Population

[37] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetic concentration of trametinib and dabrafenib

End point title	Plasma pharmacokinetic concentration of trametinib and dabrafenib

End point description:

Blood samples were collected for pharmacokinetic analysis of trametinib and dabrafenib. Data is not available and so will not be posted until October 2018.

End point type	Secondary

End point timeframe:

Pre-dose and 4, 8 hours post-dose at Weeks 2, 8 and 10

End point values	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[38]	0[39]	0[40]	
Units: Nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Nanograms per milliliter (ng/mL)	()	()	()	

Notes:

[38] - Biomarker Population.Data is not available and so will not be posted until October 2018.

[39] - Biomarker Population. Data is not available and so will not be posted until October 2018.

[40] - Biomarker Population.Data is not available and so will not be posted until October 2018.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (non-SAEs) were collected from the start of the study treatment up to 3.2 years.

Adverse event reporting additional description:

On-treatment SAEs and non-SAEs were collected in Safety Population which included all the participants who received at least one dose of randomized treatment and was based on the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Dabrafenib followed by combination therapy

Reporting group description:

Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

Reporting group title	Trametinib followed by combination therapy

Reporting group description:

Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

Reporting group title	Combination therapy

Reporting group description:

Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.

Serious adverse events	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)	7 / 16 (43.75%)	4 / 16 (25.00%)
number of deaths (all causes)	1	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma stage 0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Metastases to meninges			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Squamous cell carcinoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 16 (12.50%)	3 / 16 (18.75%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 3	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Metrorrhagia			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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			
Left ventricular dysfunction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Spinal cord compression			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Blood and lymphatic system disorders			
Histiocytosis haematophagic			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Subileus			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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			
Back pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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	Dabrafenib followed by combination therapy	Trametinib followed by combination therapy	Combination therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	16 / 16 (100.00%)	15 / 16 (93.75%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	5 / 16 (31.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	6	0	0
Papilloma			
subjects affected / exposed	3 / 16 (18.75%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Basal Cell Carcinoma			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	3
Malignant Melanoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Metastases To Meninges			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tumour Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Haemangioma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vascular disorders			
Hot Flush			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	3	0	2
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	3	3	1
Hypotension			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Haematoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Lymphoedema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Peripheral Venous Disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	5 / 16 (31.25%)	13 / 16 (81.25%)	6 / 16 (37.50%)
occurrences (all)	12	49	18
Hyperthermia			
subjects affected / exposed	4 / 16 (25.00%)	4 / 16 (25.00%)	4 / 16 (25.00%)
occurrences (all)	13	15	22
Asthenia			
subjects affected / exposed	10 / 16 (62.50%)	10 / 16 (62.50%)	9 / 16 (56.25%)
occurrences (all)	14	20	17
Chills			
subjects affected / exposed	3 / 16 (18.75%)	10 / 16 (62.50%)	4 / 16 (25.00%)
occurrences (all)	4	15	8
Oedema Peripheral			
subjects affected / exposed	4 / 16 (25.00%)	6 / 16 (37.50%)	4 / 16 (25.00%)
occurrences (all)	7	8	4
Chest Pain			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	6	2	0
Mucosal Inflammation			
subjects affected / exposed	1 / 16 (6.25%)	4 / 16 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	4	1
Influenza Like Illness			
subjects affected / exposed	3 / 16 (18.75%)	2 / 16 (12.50%)	3 / 16 (18.75%)
occurrences (all)	3	2	3
Xerosis			
subjects affected / exposed	3 / 16 (18.75%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Malaise			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Chest Discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Feeling Of Body Temperature Change			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Ill-Defined Disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Face Oedema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Inflammatory Pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Mucosal Dryness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nodule			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hernia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypothermia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oedema Due To Cardiac Disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy To Arthropod Sting			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			

Amenorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Erectile Dysfunction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal Dryness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Breast Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vaginal Haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal Pruritus			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Adenomyosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 16 (25.00%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	6	4	2
Epistaxis			
subjects affected / exposed	0 / 16 (0.00%)	4 / 16 (25.00%)	2 / 16 (12.50%)
occurrences (all)	0	5	4
Dyspnoea			
subjects affected / exposed	3 / 16 (18.75%)	3 / 16 (18.75%)	0 / 16 (0.00%)
occurrences (all)	3	3	0
Nasal Dryness			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	1	3	1
Rhinitis Allergic			

subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Dry Throat			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Dyspnoea Exertional			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Oropharyngeal Pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Pneumonitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Asthma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Catarrh			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Lower Respiratory Tract Congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Productive Cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Atelectasis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Dysphonia			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Irritability			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Mood Altered			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Sleep Disorder			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Stress			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 16 (0.00%)	5 / 16 (31.25%)	0 / 16 (0.00%)
occurrences (all)	0	15	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	1	10	1
Aspartate Aminotransferase Increased			

subjects affected / exposed	0 / 16 (0.00%)	5 / 16 (31.25%)	0 / 16 (0.00%)
occurrences (all)	0	14	0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	5 / 16 (31.25%)	7 / 16 (43.75%)	5 / 16 (31.25%)
occurrences (all)	8	9	7
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	7	0
Lipase Increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	2	4	2
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	1	3	1
C-Reactive Protein Increased			
subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Ejection Fraction Decreased			
subjects affected / exposed	0 / 16 (0.00%)	3 / 16 (18.75%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Electrocardiogram Qt Prolonged			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Weight Decreased			
subjects affected / exposed	2 / 16 (12.50%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	2	2	1
Amylase Increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Blood Triglycerides Increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Neutrophil Count Decreased			

subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	2
Intraocular Pressure Increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
White Blood Cell Count Increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood Albumin Decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Platelet Count Decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Weight Increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Blood Fibrinogen Increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Arthropod Bite			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Ligament Sprain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Limb Injury			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Procedural Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Traumatic Haematoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Palpitations			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Sinus Bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Extrasystoles			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tricuspid Valve Incompetence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Atrial Fibrillation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Mitral Valve Incompetence			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Nervous system disorders			
Headache			
subjects affected / exposed	9 / 16 (56.25%)	9 / 16 (56.25%)	6 / 16 (37.50%)
occurrences (all)	16	15	9
Tremor			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	3 / 16 (18.75%)
occurrences (all)	0	1	7
Paraesthesia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Dizziness			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	3	1	2
Hyperaesthesia			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Burning Sensation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Dysaesthesia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	2
Cervical Radiculopathy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Epilepsy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Sciatica			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Syncope			

subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Amnesia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Aphasia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Memory Impairment			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Migraine With Aura			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Presyncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Stupor			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Demyelinating Polyneuropathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Head Discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle Contractions Involuntary			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	3 / 16 (18.75%)
occurrences (all)	1	14	4
Anaemia			
subjects affected / exposed	4 / 16 (25.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	4	1	3
Eosinophilia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Lymphadenitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Histiocytosis Haematophagic			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Visual Impairment			
subjects affected / exposed	2 / 16 (12.50%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	3	2	2
Eye Pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Dry Eye			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Iridocyclitis			

subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Vision Blurred			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Eyelid Ptosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Keratitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Ocular Hyperaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Visual Acuity Reduced			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Eyelid Oedema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Uveitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Chalazion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chorioretinopathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Conjunctival Hyperaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Diplopia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vitreous Detachment			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 16 (37.50%)	7 / 16 (43.75%)	5 / 16 (31.25%)
occurrences (all)	9	19	7
Nausea			
subjects affected / exposed	8 / 16 (50.00%)	4 / 16 (25.00%)	5 / 16 (31.25%)
occurrences (all)	12	11	5
Vomiting			
subjects affected / exposed	4 / 16 (25.00%)	4 / 16 (25.00%)	3 / 16 (18.75%)
occurrences (all)	6	9	3
Constipation			
subjects affected / exposed	2 / 16 (12.50%)	5 / 16 (31.25%)	2 / 16 (12.50%)
occurrences (all)	6	6	3
Abdominal Pain			
subjects affected / exposed	2 / 16 (12.50%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	4	6	1
Abdominal Pain Upper			
subjects affected / exposed	4 / 16 (25.00%)	4 / 16 (25.00%)	0 / 16 (0.00%)
occurrences (all)	4	5	0
Abdominal Distension			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Dry Mouth			
subjects affected / exposed	2 / 16 (12.50%)	4 / 16 (25.00%)	3 / 16 (18.75%)
occurrences (all)	3	4	3
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Dysphagia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Odynophagia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	2

Aerophagia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Aphthous Ulcer			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Ascites			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gingival Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Mouth Ulceration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Painful Defaecation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rectal Haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Tooth Demineralisation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Tooth Discolouration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Anal Fissure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Food Poisoning			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Salivary Hypersecretion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tongue Discolouration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cheilitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gingival Bleeding			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatocellular Injury			
subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	1	3	2
Cholestasis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Hepatitis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 16 (25.00%)	8 / 16 (50.00%)	3 / 16 (18.75%)
occurrences (all)	5	15	3
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	6 / 16 (37.50%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	9	3	1
Palmoplantar Keratoderma			
subjects affected / exposed	7 / 16 (43.75%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	7	0	0
Alopecia			
subjects affected / exposed	4 / 16 (25.00%)	6 / 16 (37.50%)	1 / 16 (6.25%)
occurrences (all)	6	7	1
Dermatitis Acneiform			
subjects affected / exposed	0 / 16 (0.00%)	4 / 16 (25.00%)	1 / 16 (6.25%)
occurrences (all)	0	7	1
Night Sweats			
subjects affected / exposed	0 / 16 (0.00%)	3 / 16 (18.75%)	0 / 16 (0.00%)
occurrences (all)	0	5	0
Skin Lesion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	5
Erythema Nodosum			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	4	2	0
Hyperkeratosis			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	4	1	2
Keratosis Pilaris			
subjects affected / exposed	4 / 16 (25.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Dry Skin			

subjects affected / exposed	3 / 16 (18.75%)	4 / 16 (25.00%)	3 / 16 (18.75%)
occurrences (all)	3	4	3
Pruritus			
subjects affected / exposed	2 / 16 (12.50%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	2	4	3
Pigmentation Disorder			
subjects affected / exposed	3 / 16 (18.75%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Panniculitis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Erythema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	3
Onychoclasis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Rash Macular			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Skin Fissures			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	2
Hyperhidrosis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Intertrigo			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nail Dystrophy			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nail Pigmentation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypertrichosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nail Discolouration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nail Disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Prurigo			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Rash Maculo-Papular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic Dermatitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Neutrophilic Panniculitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Haematuria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Pollakiuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Renal Failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Renal Tubular Acidosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Urinary Retention			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperthyroidism			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	7 / 16 (43.75%)	4 / 16 (25.00%)	2 / 16 (12.50%)
occurrences (all)	9	5	2
Muscle Spasms			
subjects affected / exposed	5 / 16 (31.25%)	6 / 16 (37.50%)	2 / 16 (12.50%)
occurrences (all)	7	9	2
Arthralgia			
subjects affected / exposed	5 / 16 (31.25%)	3 / 16 (18.75%)	3 / 16 (18.75%)
occurrences (all)	7	8	3
Myalgia			
subjects affected / exposed	4 / 16 (25.00%)	5 / 16 (31.25%)	4 / 16 (25.00%)
occurrences (all)	5	8	7
Pain In Extremity			
subjects affected / exposed	3 / 16 (18.75%)	5 / 16 (31.25%)	3 / 16 (18.75%)
occurrences (all)	7	7	5
Neck Pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	1	6	3
Musculoskeletal Stiffness			

subjects affected / exposed	3 / 16 (18.75%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	3	5	2
Groin Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal Pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Flank Pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Limb Discomfort			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Muscle Contracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Muscular Weakness			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Spinal Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Joint Stiffness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myopathy			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 16 (6.25%)	7 / 16 (43.75%)	2 / 16 (12.50%)
occurrences (all)	1	8	2
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	5 / 16 (31.25%)	3 / 16 (18.75%)
occurrences (all)	1	5	3
Urinary Tract Infection			
subjects affected / exposed	1 / 16 (6.25%)	4 / 16 (25.00%)	3 / 16 (18.75%)
occurrences (all)	1	4	4
Bronchitis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Gastroenteritis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Rash Pustular			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0

Fungal Skin Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Paronychia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Erysipelas			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Molluscum Contagiosum			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory Syncytial Virus Infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Streptococcal Sepsis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal Candidiasis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal Mycotic Infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Fungal Oesophagitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Lung Infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Moraxella Infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Viral Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Febrile Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 16 (6.25%)	4 / 16 (25.00%)	2 / 16 (12.50%)
occurrences (all)	1	7	3
Hypocalcaemia			
subjects affected / exposed	3 / 16 (18.75%)	3 / 16 (18.75%)	1 / 16 (6.25%)
occurrences (all)	4	3	1
Hyperkalaemia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Increased Appetite			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			

subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Diabetes Mellitus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Hypomagnesaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Iron Deficiency			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vitamin D Deficiency			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Weight Fluctuation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2013	Amendment 1 - Updated figure 1 Trial design to better reflect the design of the study. - Replaced "treatment vials" with "treatment bottles" as the study drugs are tablets. - Change of brain magnetic resonance imaging (MRI) from 4 weeks to 5 weeks before Day 1. - Amendment and further clarification around the biopsies taken for this study as requested by The National Agency for the Safety of Medicines and Health Products (ANSM). This includes: a) That the biopsies were only to be done on cutaneous and subcutaneous lesions only if they are easily accessible; b) confirmation that no deep lesion biopsies were be performed; c) clarification of who is qualified to perform the biopsies. - Clarification regarding the confirmation of response. - Clarification to the pharmacokinetic blood sampling. - New France specific Appendix. - Added to reflect the monitoring required for Cutaneous Squamous Cell Carcinoma (CuSCC), new primary melanoma and non- cutaneous secondary/recurrent malignancy as requested by ANSM. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported