Clinical trial results:
A multicentre, open label, randomized Phase II trial of the MEK inhibitor pimasertib or dacarbazine in previously untreated subjects with N-Ras mutated locally advanced or metastatic malignant cutaneous melanoma

Summary

EudraCT number	2012-002669-37
Trial protocol	NL GB DE BE ES SE IT
Global end of trial date	24 October 2016

Results information

Result version number	v1 (current)
This version publication date	08 November 2017
First version publication date	08 November 2017

Trial information

Trial identification

Sponsor protocol code	EMR 200066-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01693068
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center Merck KGaA, Merck KGaA, + 49 6151 72 5200, service@merckgroup.com
Scientific contact	Communication Center Merck KGaA, Merck KGaA, + 49 6151 72 5200, service@merckgroup.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	04 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2015
Global end of trial reached?	Yes
Global end of trial date	24 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression free survival (PFS) of previously untreated subjects with N-Ras mutated locally advanced or metastatic cutaneous melanoma randomized to either pimasertib or dacarbazine treatment.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	46 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	194
EEA total number of subjects	157

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)	101
From 65 to 84 years	93
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): 05 December 2012/. Cut-off date: 04 July 2015. Last subject last visit: 24 October 2016.

Pre-assignment

Screening details:

A total of 194 subjects were randomized in trial. 64 subjects were randomized to the dacarbazine group and 130 subjects were randomized to pimasertib group. 41 of the 64 subjects randomized to dacarbazine crossed over to pimasertib treatment during the trial on progression of their disease. Data presented based on the cut-off date of 04 July 2015.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dacarbazine

Arm description:

Subjects received dacarbazine intravenously at dose of 1000 milligram per square meter (mg/m^2) of body surface area every 3 weeks on Day 1 of each 21-days cycle until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first. Eligible subjects with documented tumor progression on dacarbazine were offered to switch to pimasertib treatment. 41 of the 64 subjects randomized to dacarbazine group crossed over to pimasertib treatment during the trial on progression of their disease.

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received dacarbazine intravenously at dose of 1000 mg/m^2 of body surface area every 3 weeks on Day 1 of each 21-days cycle.

Arm title	Pimasertib

Arm description:

Subjects received pimasertib orally as monotherapy at a dose of 60 milligram (mg) twice daily continuously. Treatment consisted of repeated 21-day cycles which was continued until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first.

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

Dosage and administration details:

Pimasertib was administered as oral capsule at a dose of 60 milligram (mg) twice daily continuously.

Number of subjects in period 1	Dacarbazine	Pimasertib
Started	64	130
Treated	61	130
Completed	61	125
Not completed	3	5
On-study	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Dacarbazine

Reporting group description:

Subjects received dacarbazine intravenously at dose of 1000 milligram per square meter (mg/m^2) of body surface area every 3 weeks on Day 1 of each 21-days cycle until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first. Eligible subjects with documented tumor progression on dacarbazine were offered to switch to pimasertib treatment. 41 of the 64 subjects randomized to dacarbazine group crossed over to pimasertib treatment during the trial on progression of their disease.

Reporting group title	Pimasertib

Reporting group description:

Subjects received pimasertib orally as monotherapy at a dose of 60 milligram (mg) twice daily continuously. Treatment consisted of repeated 21-day cycles which was continued until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first.

Reporting group values	Dacarbazine	Pimasertib	Total
Number of subjects	64	130	194
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	36	65	101
>=65 years	28	65	93
Gender categorical Units: Subjects			
Female	28	62	90
Male	36	68	104

End points

End points reporting groups

Reporting group title	Dacarbazine

Reporting group description:

Subjects received dacarbazine intravenously at dose of 1000 milligram per square meter (mg/m^2) of body surface area every 3 weeks on Day 1 of each 21-days cycle until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first. Eligible subjects with documented tumor progression on dacarbazine were offered to switch to pimasertib treatment. 41 of the 64 subjects randomized to dacarbazine group crossed over to pimasertib treatment during the trial on progression of their disease.

Reporting group title	Pimasertib

Reporting group description:

Subjects received pimasertib orally as monotherapy at a dose of 60 milligram (mg) twice daily continuously. Treatment consisted of repeated 21-day cycles which was continued until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first.

Subject analysis set title	Pimaserib (Crossover)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who were randomized and received dacarbazine and were allowed to crossover to pimasertib treatment on progression of their disease.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the duration (in weeks) from randomization until the first progressive disease (PD) observation as assessed by the Investigator according to Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1, or death due to any cause when death occurred within 12 weeks after the last tumor assessment (otherwise censored), whichever occurred first. PD was defined as at least a 20% increase in the sum of diameters of the target lesions, taking as reference the smallest sum since the treatment started (including baseline), or appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions. ITT analysis set included all subjects who were randomized to trial treatment.

End point type	Primary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	130		
Units: Weeks				
median (confidence interval 95%)	6.86 (6 to 12.14)	13 (12.29 to 17.71)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The Hazard Ratio is obtained from the Cox Proportional Hazards model based on dacarbazine and

pimasertib only stratified by baseline ECOG Performance Status.

Comparison groups	Pimasertib v Dacarbazine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0022
Method	[Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.83

Notes:

[1] - A log-rank test stratified by baseline ECOG PS (using the IVRS value) will tested the null hypothesis of no difference between the Pimasertib (first line) and the Dacarbazine treatment groups at the 5% level.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of subjects with complete response (CR) or partial response (PR) according to RECIST version 1.1 criteria. CR: defined as disappearance of all target and all non-target lesions. 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 a 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters along with absence of new lesions and disease progression in non-target lesions. ITT analysis set included all subjects who were randomised to trial treatment.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	130		
Units: percentage of subjects				
number (confidence interval 95%)	14.1 (6.6 to 25)	26.9 (19.5 to 35.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR was defined as the percentage of subjects with CR, PR, or stable disease (SD) for greater than (>)

3 months assessed by investigator according to RECIST version 1.1. CR: defined as disappearance of all target and all non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than <10 mm. PR: defined as at least a 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters along with absence of new lesions and disease progression in non-target lesions. SD: defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. ITT analysis set included all subjects who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	130		
Units: percentage of subjects				
number (confidence interval 95%)	15.6 (7.8 to 26.9)	33.1 (25.1 to 41.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Progression-free Survival (PFS) at 6 Months

End point title	Percentage of Subjects With Progression-free Survival (PFS) at 6 Months

End point description:

PFS was defined as the duration (in weeks) from randomization until the first progressive disease (PD) observation as assessed by the Investigator according to Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1, or death due to any cause when death occurred within 12 weeks after the last tumor assessment, whichever occurred first. PD was defined as at least a 20% increase in the sum of diameters of the target lesions, taking as reference the smallest sum since the treatment started (including baseline), or appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions. Percentage of Subjects with PFS at 6 Months were reported. ITT analysis set included all subjects who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	130		
Units: percentage of subjects				
number (confidence interval 95%)	9.4 (3.6 to 18.6)	17.3 (10.2 to 26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time (in months) from randomization to death due to any cause. Subjects without a death date were to be censored at the minimum of last known date alive, defined as the latest date available on the electronic case report form, and cut-off date. ITT analysis set included all subjects who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

From date of randomization until date of death from any cause, assessed up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	130		
Units: months				
median (confidence interval 95%)	10.61 (7.26 to 16.49)	8.87 (7.46 to 15.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Survival (OS) at 12 Months

End point title	Percentage of Subjects With Overall Survival (OS) at 12 Months

End point description:

OS was defined as the time (in months) from randomization to death due to any cause. Subjects without a death date were to be censored at the minimum of last known date alive, defined as the latest date available on the electronic case report form, and cut-off date. Percentage of Subjects with OS at 12 months were reported. ITT analysis set included all subjects who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

12 months

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	130		
Units: percentage of subjects				
number (confidence interval 95%)	44.5 (31.6 to 56.6)	43.3 (34.5 to 51.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject-reported Quality of Life Assessed by Functional Assessment Cancer Therapy - Melanoma Total Score (FACT-M TS) at Day 1 of Pre-Specified Cycles and End of Treatment (EOT)

End point title	Change From Baseline in Subject-reported Quality of Life Assessed by Functional Assessment Cancer Therapy - Melanoma Total Score (FACT-M TS) at Day 1 of Pre-Specified Cycles and End of Treatment (EOT)

End point description:

QoL assessed using FACT-M assessment tool. This includes 27-item FACT-G questionnaire which consists of 24 questions; 7 relating to PWB, 7 relating to SWB,6 relating to EWB and 7 relating to FWB. Also, it includes melanoma-specific subscale consists of 16 questions for MS and 8 questions for MSS. Each of these questions could have a response of Not at all, a little bit, somewhat, quite a bit and very much. The responses were given a value between 0 and 4 with 4 being best response. The FACT-M TS ranges from 0 to 172 and is derived as follows: FACT-M TS= PWB Score + SWB Score + EWB Score + FWB Score + MS Score. Higher scores represent a better quality of life. Here "99999" signifies data was not available for categories with n=1 because standard deviation could not be estimated if there was only 1 subject analysed and "99999"signifies data was not available for categories with n=0 because there were no subject analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 35, 36, 37 and EOT (up to cut-off date [04-Jul-2015])

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[2]	126[3]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=58, 126)	126.2 (± 23.828)	132.24 (± 22.179)		
Change at Day 1 Cycle 2 (n=45, 99)	-3.05 (± 14.815)	-3.06 (± 18.492)		
Change at Day 1 Cycle 3 (n=24, 73)	0.6 (± 19.965)	-6.77 (± 21.716)		
Change at Day 1 Cycle 4 (n=23, 63)	4.11 (± 14.746)	-6.54 (± 19.919)		
Change at Day 1 Cycle 5 (n=10, 45)	0.62 (± 11.81)	-2.81 (± 17.202)		
Change at Day 1 Cycle 6 (n=9, 33)	-3.71 (± 15.674)	-8.45 (± 20.939)		

Change at Day 1 Cycle 7 (n=9, 29)	-1.1 (± 13.318)	-8.84 (± 19.128)		
Change at Day 1 Cycle 8 (n=8, 18)	1.28 (± 12.928)	-14.67 (± 18.508)		
Change at Day 1 Cycle 9 (n=6, 12)	2.21 (± 16.224)	-13.67 (± 21.388)		
Change at Day 1 Cycle 10 (n=6, 10)	4.4 (± 14.818)	-13.26 (± 20.716)		
Change at Day 1 Cycle 11 (n=4, 11)	1.02 (± 19.161)	-14.1 (± 21.157)		
Change at Day 1 Cycle 12 (n=4, 11)	1.56 (± 19.932)	-10.52 (± 18.895)		
Change at Day 1 Cycle 13 (n=4, 6)	5.51 (± 20.191)	-13.38 (± 23.69)		
Change at Day 1 Cycle 14 (n=2,8)	11.5 (± 21.92)	-18.24 (± 22.998)		
Change at Day 1 Cycle 15 (n=3, 7)	9.6 (± 15.345)	-11.33 (± 19.787)		
Change at Day 1 Cycle 16 (n=3, 7)	10.56 (± 14.935)	-11.18 (± 23.68)		
Change at Day 1 Cycle 17 (n=2, 6)	3 (± 5.657)	-9.18 (± 24.166)		
Change at Day 1 Cycle 18 (n=1, 5)	27 (± 99999)	-3.92 (± 9.64)		
Change at Day 1 Cycle 19 (n=2, 4)	16.5 (± 14.849)	-1.15 (± 8.147)		
Change at Day 1 Cycle 20 (n=2, 3)	16 (± 15.556)	1.17 (± 5.947)		
Change at Day 1 Cycle 21 (n=2, 3)	17 (± 14.142)	4.17 (± 8.918)		
Change at Day 1 Cycle 22 (n=2, 3)	18 (± 12.728)	1.32 (± 11.163)		
Change at Day 1 Cycle 23 (n=1, 2)	27 (± 99999)	-13.69 (± 15.354)		
Change at Day 1 Cycle 24 (n=2, 1)	13.5 (± 19.092)	-3.83 (± 99999)		
Change at Day 1 Cycle 25 (n=2, 1)	14.5 (± 17.678)	-3.83 (± 99999)		
Change at Day 1 Cycle 26 (n=1, 1)	27 (± 99999)	-2.83 (± 99999)		
Change at Day 1 Cycle 27 (n=1, 0)	27 (± 99999)	99999 (± 99999)		
Change at Day 1 Cycle 28 (n=1, 1)	27 (± 99999)	-0.83 (± 99999)		
Change at Day 1 Cycle 30 (n=0, 1)	99999 (± 99999)	-1.83 (± 99999)		
Change at Day 1 Cycle 31 (n=0, 1)	99999 (± 99999)	-7.83 (± 99999)		
Change at Day 1 Cycle 32 (n=0, 1)	99999 (± 99999)	-7.83 (± 99999)		
Change at Day 1 Cycle 33 (n=0, 1)	99999 (± 99999)	-8.83 (± 99999)		
Change at Day 1 Cycle 35 (n=0, 1)	99999 (± 99999)	-1.83 (± 99999)		
Change at Day 1 Cycle 36 (n=0, 1)	99999 (± 99999)	-3.83 (± 99999)		
Change at Day 1 Cycle 37 (n=0, 1)	99999 (± 99999)	-4.83 (± 99999)		
Change at EOT (n=28, 75)	-7.91 (± 23.119)	-9.98 (± 20.56)		

Notes:

[2] - Number of subjects = those evaluable for this outcome. n=subjects evaluable at each time point.

[3] - Number of subjects = those evaluable for this outcome. n=subjects evaluable at each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject-reported Quality of Life Assessed by Functional Assessment Cancer Therapy - Melanoma Trial Outcome Index (FACT-M TOI) at Day 1 of Pre-Specified Cycles and EOT

End point title	Change From Baseline in Subject-reported Quality of Life Assessed by Functional Assessment Cancer Therapy - Melanoma Trial Outcome Index (FACT-M TOI) at Day 1 of Pre-Specified Cycles and EOT

End point description:

QoL assessed using FACT-M assessment tool. This includes 27-item FACT-G questionnaire which consists of 24 questions; 7 relating to PWB, 7 relating to SWB, 6 relating to EWB and 7 relating to FWB. Also, it includes melanoma-specific subscale consists of 16 questions for MS and 8 questions for the MSS. Each of these questions could have a response of Not at all, a little bit, somewhat, quite a bit and very much. The responses were given a value between 0 and 4 with 4 being best response. The FACT-M Trial Outcome Index (FACT-M TOI) ranges from 0 to a high of 120 and is derived as: FACT-M TOI = PWB Score + FWB Score +MS Score. Higher scores represent a better quality of life. Here "99999" signifies data was not available for categories with n=1 because standard deviation could not be estimated if there was only 1 subject analysed and "99999"signifies data was not available for categories with n=0 because there were no subjects analyzed at specified time point for those categories.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 35, 36, 37 and EOT (up to cut-off date [04-Jul-2015])

End point values	Dacarbazine	Pimasertib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[4]	126[5]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=58, 126)	90.35 (± 19.348)	94.07 (± 17.534)		
Change at Day 1 Cycle 2 (n=45, 99)	-3.33 (± 12.015)	-4.4 (± 14.286)		
Change at Day 1 Cycle 3 (n=24, 73)	-0.69 (± 15.974)	-7.99 (± 17.089)		
Change at Day 1 Cycle 4 (n=23, 63)	1.54 (± 10.304)	-7.97 (± 16.741)		
Change at Day 1 Cycle 5 (n=10, 45)	-0.86 (± 5.405)	-4.37 (± 14.084)		
Change at Day 1 Cycle 6 (n=9, 33)	-3.29 (± 7.752)	-9.15 (± 18.813)		
Change at Day 1 Cycle 7 (n=9, 29)	-2.07 (± 6.859)	-8.99 (± 14.783)		
Change at Day 1 Cycle 8 (n=8, 18)	0.83 (± 5.161)	-15.09 (± 14.458)		
Change at Day 1 Cycle 9 (n=6, 12)	-1.93 (± 6.3)	-13.79 (± 17.198)		
Change at Day 1 Cycle 10 (n=6, 10)	-1.1 (± 5.654)	-12.37 (± 17.058)		
Change at Day 1 Cycle 11 (n=4, 11)	-2.9 (± 7.722)	-13.95 (± 17.006)		
Change at Day 1 Cycle 12 (n=4, 11)	-2.4 (± 7.408)	-11.95 (± 17.311)		

Change at Day 1 Cycle 13 (n=4, 6)	0.8 (± 7.697)	-13.57 (± 21.699)		
Change at Day 1 Cycle 14 (n=2, 8)	0 (± 4.243)	-18.55 (± 19.88)		
Change at Day 1 Cycle 15 (n=3, 7)	1.6 (± 4.084)	-13.59 (± 15.747)		
Change at Day 1 Cycle 16 (n=3, 7)	0.61 (± 3.994)	-13.15 (± 19.13)		
Change at Day 1 Cycle 17 (n=2, 6)	2.5 (± 0.707)	-10.66 (± 20.007)		
Change at Day 1 Cycle 18 (n=1, 5)	3 (± 99999)	-5.72 (± 4.614)		
Change at Day 1 Cycle 19 (n=2, 4)	2.5 (± 0.707)	-4.94 (± 5.238)		
Change at Day 1 Cycle 20 (n=2, 3)	4 (± 1.414)	-2.33 (± 1.155)		
Change at Day 1 Cycle 21 (n=2, 3)	3.5 (± 0.707)	0 (± 2)		
Change at Day 1 Cycle 22 (n=2, 3)	4 (± 1.414)	-1.4 (± 3.831)		
Change at Day 1 Cycle 23 (n=1, 2)	3 (± 99999)	-13.36 (± 16.061)		
Change at Day 1 Cycle 24 (n=2, 1)	2.5 (± 0.707)	-2 (± 99999)		
Change at Day 1 Cycle 25 (n=2, 1)	3.5 (± 0.707)	-1 (± 99999)		
Change at Day 1 Cycle 26 (n=1, 1)	3 (± 99999)	0 (± 99999)		
Change at Day 1 Cycle 27 (n=1, 0)	3 (± 99999)	99999 (± 99999)		
Change at Day 1 Cycle 28 (n=1, 1)	3 (± 99999)	1 (± 99999)		
Change at Day 1 Cycle 30 (n=0, 1)	99999 (± 99999)	1 (± 99999)		
Change at Day 1 Cycle 31 (n=0, 1)	99999 (± 99999)	-3 (± 99999)		
Change at Day 1 Cycle 32 (n=0, 1)	99999 (± 99999)	-4 (± 99999)		
Change at Day 1 Cycle 33 (n=0, 1)	99999 (± 99999)	-3 (± 99999)		
Change at Day 1 Cycle 35 (n=0, 1)	99999 (± 99999)	0 (± 99999)		
Change at Day 1 Cycle 36 (n=0, 1)	99999 (± 99999)	0 (± 99999)		
Change at Day 1 Cycle 37 (n=0, 1)	99999 (± 99999)	-3 (± 99999)		
Change at EOT (n=28, 75)	-8.18 (± 16.41)	-10.42 (± 16.256)		

Notes:

[4] - Number of subjects = those evaluable for this outcome. n=subjects evaluable at each time point.

[5] - Number of subjects = those evaluable for this outcome. n=subjects evaluable at each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Discontinuation or TEAEs Leading to Death

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Discontinuation or TEAEs Leading to Death

End point description:

AE was defined as any untoward medical occurrence which does not necessarily have causal relationship with this study drug. An AE was defined as any unfavourable and unintended sign(including an abnormal laboratory finding, vital signs electrocardiogram changes), symptom, or disease temporally associated

with use of study drug, whether or not considered related to the study drug. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening;persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent are events between first dose of study drug and up to 33 days after last dose that were absent before treatment or that worsened relative to pre-treatment state. TEAEs include both Serious TEAEs and non-serious TEAEs. TEAEs were to be reported separately for dacarbazine, pimasertib and pimasertib (crossover) reporting arms.

End point type	Secondary

End point timeframe:

Baseline up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib	Pimaserib (Crossover)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	130	41	
Units: subjects				
number (not applicable)				
Retinal vein occlusion	0	5	2	
Serious retinal detatchment	0	76	21	
CPK/Isoenzyme TEAE of Special Interest (>=Grade 2)	0	74	24	
Acute renal failure (Grade >= 2)	1	9	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Laboratory Parameter, Vital Signs, Electrocardiogram (ECG) and Ophthalmologic Findings

End point title	Number of Subjects With Clinically Significant Change From Baseline in Laboratory Parameter, Vital Signs, Electrocardiogram (ECG) and Ophthalmologic Findings

End point description:

Subjects were presented under 3 reporting groups: Dacarbazine group: for subjects who received at least 1 dose of dacarbazine; Pimasertib group: for subjects who received at least 1 dose of pimasertib; Pimasertib (Crossover) group: for subjects who were initially randomized and received dacarbazine, but crossed over to pimasertib treatment on progression of their disease.

End point type	Secondary

End point timeframe:

Baseline up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib	Pimaserib (Crossover)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	130	41	
Units: number of subjects				
Laboratory Parameter	0	0	0	
Vital Signs	0	0	0	
ECG	0	0	0	
Ophthalmologic Findings	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) of Special interest

End point title	Number of Subjects With Adverse Events (AEs) of Special interest

End point description:

Adverse events of special interest included ocular TEAEs, creatinine phosphokinase (CPK) Elevation and Isoenzymes TEAEs and CPK Elevation and Isoenzymes TEAEs with Grade 2 or higher. Subjects were presented under 3 reporting groups: Dacarbazine group: for subjects who received at least 1 dose of dacarbazine; Pimasertib group: for subjects who received at least 1 dose of pimasertib; Pimasertib (Crossover) group: for subjects who were initially randomized and received dacarbazine, but crossed over to pimasertib treatment on progression of their disease.

End point type	Secondary

End point timeframe:

Baseline up to cut-off date (04-Jul-2015)

End point values	Dacarbazine	Pimasertib	Pimaserib (Crossover)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	130	41	
Units: number of subjects				
Ocular TEAE of Special Interest	0	76	21	
CPK Elevation/Isoenzymes TEAE of Special Interest	3	89	29	
CPK/Isoenzyme TEAE of Special Interest (>=Grade 2)	0	74	24	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to cut-off date (04-Jul-2015)

Adverse event reporting additional description:

Subjects presented under 3 reporting groups: Dacarbazine: for subjects who received at least 1 dose of dacarbazine; Pimasertib: for subjects who received at least 1 dose of pimasertib; Pimasertib (Crossover): for subjects who were initially randomized and received dacarbazine, but crossed over to pimasertib treatment on disease progression.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Dacarbazine

Reporting group description:

Subjects received dacarbazine intravenously at dose of 1000 mg/m^2 of body surface area every 3 weeks on Day 1 of each 21-days cycle until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first. Eligible subjects with documented tumor progression on dacarbazine were offered to switch to pimasertib treatment.

Reporting group title	Pimasertib

Reporting group description:

Subjects received pimasertib orally as monotherapy at a dose of 60 mg twice daily continuously. Treatment consisted of repeated 21-day cycles which was continued until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death, whichever occurred first.

Reporting group title	Pimasertib (Crossover)

Reporting group description:

Subjects who were randomized and received dacarbazine and were allowed to crossover to pimasertib treatment on progression of their disease.

Serious adverse events	Dacarbazine	Pimasertib	Pimasertib (Crossover)
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 61 (19.67%)	74 / 130 (56.92%)	26 / 41 (63.41%)
number of deaths (all causes)	4	6	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (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
Hypertension			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Hypotension			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
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			
Chest pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Chills			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Cyst rupture			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Death			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Disease progression			

subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	1 / 1
Fatigue			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
General physical health deterioration			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	4 / 41 (9.76%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Impaired healing			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Malaise			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Oedema peripheral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (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			
Dyspnoea			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 61 (0.00%)	26 / 130 (20.00%)	8 / 41 (19.51%)
occurrences causally related to treatment / all	0 / 0	25 / 26	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Troponin increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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			
Subdural haematoma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Atrial fibrillation			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cor pulmonale acute			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Left ventricular dysfunction			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Pericarditis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (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
Nervous system disorders			

Ataxia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Epilepsy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Neuralgia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Presyncope			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Leukocytosis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 61 (4.92%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystoid macular oedema			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular detachment			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			

subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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			
Abdominal pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (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
Constipation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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 / 61 (1.64%)	6 / 130 (4.62%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	1 / 1	4 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (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
Mouth ulceration			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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	1 / 61 (1.64%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	1 / 1	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Hepatotoxicity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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 and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Rash macular			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Rash maculo−papular			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
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 toxicity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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			
Urinary retention			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal mass			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Muscular weakness			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain in extremity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Pathological fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (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 column stenosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Candida infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Catheter site infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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 / 61 (0.00%)	7 / 130 (5.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Localised infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Pharyngitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Sepsis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Streptococcal sepsis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Hyponatraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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
Tumour lysis syndrome			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dacarbazine	Pimasertib	Pimasertib (Crossover)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 61 (96.72%)	130 / 130 (100.00%)	41 / 41 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Blepharal papilloma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Breast neoplasm			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Cancer pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Malignant melanoma			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Metastatic pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Monoclonal gammopathy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pyogenic granuloma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin cancer			

subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Skin papilloma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Squamous cell carcinoma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Tumour haemorrhage			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Tumour pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Deep vein thrombosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Diastolic hypertension			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	2 / 61 (3.28%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Haematoma			
subjects affected / exposed	2 / 61 (3.28%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	2	1	0
Hot flush			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 61 (3.28%)	21 / 130 (16.15%)	6 / 41 (14.63%)
occurrences (all)	2	21	6

Hypotension			
subjects affected / exposed	3 / 61 (4.92%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	3	4	2
Lymphoedema			
subjects affected / exposed	2 / 61 (3.28%)	11 / 130 (8.46%)	3 / 41 (7.32%)
occurrences (all)	2	11	3
Pelvic venous thrombosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Peripheral coldness			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Peripheral ischaemia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Peripheral venous disease			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Phlebitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Vascular compression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Vena cava thrombosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	13 / 61 (21.31%)	39 / 130 (30.00%)	10 / 41 (24.39%)
occurrences (all)	13	39	10
Axillary pain			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	1	1	1
Catheter site pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	3 / 61 (4.92%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	3	2	1
Chills			
subjects affected / exposed	3 / 61 (4.92%)	11 / 130 (8.46%)	3 / 41 (7.32%)
occurrences (all)	3	11	3
Crying			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Disease progression			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Drug intolerance			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Enanthema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 61 (0.00%)	12 / 130 (9.23%)	9 / 41 (21.95%)
occurrences (all)	5	12	9
Facial pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1

Fatigue			
subjects affected / exposed	23 / 61 (37.70%)	39 / 130 (30.00%)	11 / 41 (26.83%)
occurrences (all)	23	39	11
Feeling cold			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Gait disturbance			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Generalised oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hyperpyrexia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hyperthermia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Hypothermia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Inflammation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	1	3	0
Injection site haematoma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Malaise			
subjects affected / exposed	2 / 61 (3.28%)	5 / 130 (3.85%)	2 / 41 (4.88%)
occurrences (all)	2	5	2
Mucosal dryness			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Non−cardiac chest pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Oedema			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Oedema peripheral			
subjects affected / exposed	6 / 61 (9.84%)	59 / 130 (45.38%)	18 / 41 (43.90%)
occurrences (all)	6	59	18
Pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Papillitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	2 / 41 (4.88%)
occurrences (all)	0	5	2
Pyrexia			
subjects affected / exposed	5 / 61 (8.20%)	27 / 130 (20.77%)	10 / 41 (24.39%)
occurrences (all)	5	27	10
Secretion discharge			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Sensation of foreign body			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Temperature intolerance			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1

Vessel puncture site haematoma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site inflammation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Xerosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Genital discomfort			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Genital erythema			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Haematospermia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pelvic pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Scrotal haematocoele			

subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Scrotal oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Asthma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Atelectasis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Bronchospasm			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	5 / 61 (8.20%)	9 / 130 (6.92%)	3 / 41 (7.32%)
occurrences (all)	5	9	3
Dry throat			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Dysphonia			
subjects affected / exposed	1 / 61 (1.64%)	5 / 130 (3.85%)	1 / 41 (2.44%)
occurrences (all)	1	5	1
Dyspnoea			
subjects affected / exposed	4 / 61 (6.56%)	26 / 130 (20.00%)	6 / 41 (14.63%)
occurrences (all)	4	26	6
Dyspnoea exertional			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	1	4	1
Epistaxis			

subjects affected / exposed	2 / 61 (3.28%)	8 / 130 (6.15%)	2 / 41 (4.88%)
occurrences (all)	2	8	2
Hiccups			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hypoventilation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Lung disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Nasal oedema			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Nocturnal dyspnoea			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	3 / 41 (7.32%)
occurrences (all)	1	4	3
Nasal disorder			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Orthopnoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pharyngeal ulceration			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			

subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	1	4	0
Pneumonitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Productive cough			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	2 / 41 (4.88%)
occurrences (all)	1	2	2
Rales			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Respiratory disorder			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Rhinalgia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Throat irritation			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Wheezing			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			

Agitation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	6 / 61 (9.84%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	6	3	2
Confusional state			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Depressed mood			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Dyssomnia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Euphoric mood			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hallucination, visual			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	4 / 61 (6.56%)	7 / 130 (5.38%)	1 / 41 (2.44%)
occurrences (all)	4	7	1
Irritability			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Mood altered			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0

Nervousness			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Persecutory delusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Psychomotor retardation			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 61 (6.56%)	6 / 130 (4.62%)	1 / 41 (2.44%)
occurrences (all)	4	6	1
Amylase increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 61 (4.92%)	17 / 130 (13.08%)	4 / 41 (9.76%)
occurrences (all)	3	17	4
Blood albumin decreased			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 61 (3.28%)	5 / 130 (3.85%)	3 / 41 (7.32%)
occurrences (all)	2	5	3
Blood bicarbonate decreased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Blood bilirubin increased			

subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 61 (4.92%)	86 / 130 (66.15%)	28 / 41 (68.29%)
occurrences (all)	3	86	28
Blood creatinine increased			
subjects affected / exposed	2 / 61 (3.28%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	2	2	1
Blood fibrinogen decreased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences (all)	1	3	1
Blood phosphorus increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood potassium increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Blood urea increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Breath sounds abnormal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
C−reactive protein increased			

subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Ejection fraction decreased			
subjects affected / exposed	0 / 61 (0.00%)	13 / 130 (10.00%)	3 / 41 (7.32%)
occurrences (all)	0	13	3
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QRS complex prolonged			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	0	4	1
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 61 (3.28%)	4 / 130 (3.08%)	3 / 41 (7.32%)
occurrences (all)	2	4	3
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Intraocular pressure increased			

subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences (all)	0	3	1
Lipase increased			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	2 / 41 (4.88%)
occurrences (all)	1	2	2
Lymphocyte count decreased			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	0 / 41 (0.00%)
occurrences (all)	0	5	0
Neutrophil count decreased			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	1	3	0
Oxygen saturation decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	1 / 61 (1.64%)	6 / 130 (4.62%)	1 / 41 (2.44%)
occurrences (all)	1	6	1
Protein total decreased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Protein total increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pupillary light reflex tests abnormal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Troponin increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	2 / 61 (3.28%)	8 / 130 (6.15%)	3 / 41 (7.32%)
occurrences (all)	2	8	3
Weight increased			
subjects affected / exposed	0 / 61 (0.00%)	9 / 130 (6.92%)	2 / 41 (4.88%)
occurrences (all)	0	9	2
White blood cell count decreased			

subjects affected / exposed	2 / 61 (3.28%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	2	2	0
White blood cell count increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Clavicle fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Concussion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Excoriation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Lip injury			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Muscle strain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Optic nerve injury			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Rib fracture			

subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Scratch			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Spinal compression fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Tendon rupture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Traumatic shock			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Wound complication			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Optic nerve hypoplasia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Ventricular septal defec			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Aortic valve disease			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Aortic valve incompetence			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Aortic valve stenosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	2 / 61 (3.28%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	2	2	0
Atrioventricular block			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Atrioventricular block first degree			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Atrioventricular block second degree			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Bundle branch block			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Bundle branch block right			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Diastolic dysfunction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Left ventricular hypertrophy			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Mitral valve incompetence			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	0	4	2
Mitral valve sclerosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Pericardial effusion			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Pulmonary valve incompetence			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Tachycardia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Tricuspid valve incompetence			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	4 / 41 (9.76%)
occurrences (all)	0	5	4
Ventricular hypokinesia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Nervous system disorders			

Ageusia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Altered state of consciousness			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Amnesia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Aphasia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Ataxia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Balance disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Depressed level of consciousness			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	3 / 61 (4.92%)	17 / 130 (13.08%)	5 / 41 (12.20%)
occurrences (all)	3	17	5
Dizziness postural			

subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Dysaesthesia			
subjects affected / exposed	4 / 61 (6.56%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	4	1	0
Dysarthria			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Dysgeusia			
subjects affected / exposed	6 / 61 (9.84%)	11 / 130 (8.46%)	4 / 41 (9.76%)
occurrences (all)	6	11	4
Headache			
subjects affected / exposed	8 / 61 (13.11%)	16 / 130 (12.31%)	0 / 41 (0.00%)
occurrences (all)	8	16	0
Hyperaesthesia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	2 / 41 (4.88%)
occurrences (all)	1	1	2
Lethargy			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Loss of consciousness			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Memory impairment			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	1 / 41 (2.44%)
occurrences (all)	0	5	1
Migraine			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Motor dysfunction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Muscle contractions involuntary			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Myasthenic syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Neurotoxicity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	9 / 61 (14.75%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	9	4	2
Peripheral motor neuropathy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Presyncope			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Sciatica			
subjects affected / exposed	3 / 61 (4.92%)	5 / 130 (3.85%)	3 / 41 (7.32%)
occurrences (all)	3	5	3
Sensorimotor disorder			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Sensory disturbance			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Somnolence			
subjects affected / exposed	0 / 61 (0.00%)	6 / 130 (4.62%)	1 / 41 (2.44%)
occurrences (all)	0	6	1
Syncope			

subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	0	4	1
Tremor			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Visual field defect			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Hypochromic anaemia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Increased tendency to bruise			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Leukocytosis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Leukopenia			
subjects affected / exposed	6 / 61 (9.84%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	6	1	0
Lymph node pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Lymphadenitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Lymphocytosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Lymphopenia			
subjects affected / exposed	1 / 61 (1.64%)	9 / 130 (6.92%)	2 / 41 (4.88%)
occurrences (all)	1	9	2
Neutropenia			
subjects affected / exposed	13 / 61 (21.31%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	13	1	0
Normochromic normocytic anaemia			
subjects affected / exposed	2 / 61 (3.28%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	2	2	1
Thrombocytopenia			
subjects affected / exposed	12 / 61 (19.67%)	8 / 130 (6.15%)	3 / 41 (7.32%)
occurrences (all)	12	8	3
Thrombocytosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	8 / 61 (13.11%)	13 / 130 (10.00%)	3 / 41 (7.32%)
occurrences (all)	8	13	3
Anaemia of chronic disease			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Ear congestion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Hypoacusis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Middle ear inflammation			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Vertigo			
subjects affected / exposed	2 / 61 (3.28%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	2	3	0
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blindness			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Chalazion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Chorioretinopathy			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Chromatopsia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Colour blindness acquired			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Conjunctival haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Conjunctival oedema			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0

Cystoid macular oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Deposit eye			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Diplopia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	1 / 61 (1.64%)	5 / 130 (3.85%)	0 / 41 (0.00%)
occurrences (all)	1	5	0
Erythema of eyelid			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Eye discharge			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Eye disorder			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Eye haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Eye inflammation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Eye oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Eye pain			

subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	1	3	0
Eye pruritus			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Eyelid haematoma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Eyelid oedema			
subjects affected / exposed	1 / 61 (1.64%)	18 / 130 (13.85%)	2 / 41 (4.88%)
occurrences (all)	1	18	2
Eyelid ptosis			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Glaucoma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Macular cyst			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Macular degeneration			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Macular detachment			
subjects affected / exposed	0 / 61 (0.00%)	10 / 130 (7.69%)	2 / 41 (4.88%)
occurrences (all)	0	10	2
Macular fibrosis			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Macular oedema			

subjects affected / exposed	0 / 61 (0.00%)	6 / 130 (4.62%)	1 / 41 (2.44%)
occurrences (all)	0	6	1
Myopia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Ocular hypertension			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Optic disc haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Periorbital oedema			
subjects affected / exposed	0 / 61 (0.00%)	12 / 130 (9.23%)	1 / 41 (2.44%)
occurrences (all)	0	12	1
Photophobia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Photopsia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Presbyopia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Retinal deposits			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Retinal detachment			
subjects affected / exposed	0 / 61 (0.00%)	56 / 130 (43.08%)	15 / 41 (36.59%)
occurrences (all)	0	56	15
Retinal disorder			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Retinal haemorrhage			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Retinal oedema			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Retinal pigment epitheliopathy			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Retinal vein occlusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Retinopathy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Subretinal fluid			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Vision blurred			
subjects affected / exposed	0 / 61 (0.00%)	29 / 130 (22.31%)	9 / 41 (21.95%)
occurrences (all)	0	29	9
Visual acuity reduced			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	0 / 41 (0.00%)
occurrences (all)	0	5	0
Visual impairment			
subjects affected / exposed	0 / 61 (0.00%)	12 / 130 (9.23%)	2 / 41 (4.88%)
occurrences (all)	0	12	2
Vitreous detachment			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Vitreous floaters			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Xerophthalmia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	1	4	2
Abdominal pain			
subjects affected / exposed	10 / 61 (16.39%)	31 / 130 (23.85%)	7 / 41 (17.07%)
occurrences (all)	10	31	7
Abdominal pain upper			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Abdominal pain lower			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Anal polyp			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Aphthous stomatitis			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	0	4	2
Aptyalism			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Ascites			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Cheilitis			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	0	4	1
Colitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	21 / 61 (34.43%)	24 / 130 (18.46%)	7 / 41 (17.07%)
occurrences (all)	21	24	7
Diarrhoea			
subjects affected / exposed	10 / 61 (16.39%)	106 / 130 (81.54%)	31 / 41 (75.61%)
occurrences (all)	10	106	31

Dry mouth			
subjects affected / exposed	2 / 61 (3.28%)	20 / 130 (15.38%)	8 / 41 (19.51%)
occurrences (all)	2	20	8
Duodenal ulcer			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 61 (0.00%)	11 / 130 (8.46%)	3 / 41 (7.32%)
occurrences (all)	0	11	3
Dysphagia			
subjects affected / exposed	1 / 61 (1.64%)	5 / 130 (3.85%)	2 / 41 (4.88%)
occurrences (all)	1	5	2
Epigastric discomfort			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Faeces discoloured			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Flatulence			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Gastric ulcer			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Gastritis erosive			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 61 (3.28%)	5 / 130 (3.85%)	2 / 41 (4.88%)
occurrences (all)	2	5	2
Glossitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1

Glossodynia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Haematemesis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Haemorrhoids			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	1	4	1
Hyperchlorhydria			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Intestinal obstruction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Lip oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Lip pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Melaena			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Mouth swelling			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 61 (0.00%)	7 / 130 (5.38%)	1 / 41 (2.44%)
occurrences (all)	0	7	1
Nausea			
subjects affected / exposed	25 / 61 (40.98%)	47 / 130 (36.15%)	17 / 41 (41.46%)
occurrences (all)	25	47	17
Odynophagia			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Oesophagitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral discomfort			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral dysaesthesia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral mucosal eruption			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral mucosal erythema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral pruritus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral toxicity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Paraesthesia oral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	8 / 130 (6.15%)	1 / 41 (2.44%)
occurrences (all)	0	8	1
Regurgitation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	3 / 61 (4.92%)	21 / 130 (16.15%)	4 / 41 (9.76%)
occurrences (all)	3	21	4
Subileus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Tongue disorder			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Tongue oedema			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Tongue ulceration			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Toothache			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Umbilical hernia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	14 / 61 (22.95%)	30 / 130 (23.08%)	16 / 41 (39.02%)
occurrences (all)	14	30	16

Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	1	4	0
Hepatic pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hepatocellular injury			
subjects affected / exposed	0 / 61 (0.00%)	7 / 130 (5.38%)	0 / 41 (0.00%)
occurrences (all)	0	7	0
Hepatomegaly			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	3 / 41 (7.32%)
occurrences (all)	0	4	3
Alopecia			
subjects affected / exposed	2 / 61 (3.28%)	13 / 130 (10.00%)	4 / 41 (9.76%)
occurrences (all)	2	13	4
Decubitus ulcer			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences (all)	0	3	1
Dermatitis acneiform			
subjects affected / exposed	0 / 61 (0.00%)	47 / 130 (36.15%)	9 / 41 (21.95%)
occurrences (all)	0	47	9
Dermatitis exfoliative			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	2 / 41 (4.88%)
occurrences (all)	0	2	2
Diffuse alopecia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Drug eruption			

subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	1 / 61 (1.64%)	11 / 130 (8.46%)	3 / 41 (7.32%)
occurrences (all)	1	11	3
Eczema			
subjects affected / exposed	0 / 61 (0.00%)	8 / 130 (6.15%)	1 / 41 (2.44%)
occurrences (all)	0	8	1
Erythema			
subjects affected / exposed	2 / 61 (3.28%)	14 / 130 (10.77%)	4 / 41 (9.76%)
occurrences (all)	2	14	4
Erythrosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Hair growth abnormal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hirsutism			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	2 / 61 (3.28%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	2	2	0
Hyperkeratosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Ingrowing nail			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Intertrigo			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	1	4	0
Nail bed inflammation			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Nail disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Onycholysis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pain of skin			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Palmar−plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 61 (0.00%)	6 / 130 (4.62%)	0 / 41 (0.00%)
occurrences (all)	0	6	0
Papule			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Petechiae			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	2 / 61 (3.28%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	2	3	0
Pigmentation disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Prurigo			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Pruritus			
subjects affected / exposed	1 / 61 (1.64%)	17 / 130 (13.08%)	7 / 41 (17.07%)
occurrences (all)	1	17	7
Pruritus generalised			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Psoriasis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	5 / 61 (8.20%)	46 / 130 (35.38%)	18 / 41 (43.90%)
occurrences (all)	5	46	18
Rash erythematous			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	2 / 41 (4.88%)
occurrences (all)	0	4	2
Rash generalised			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	1 / 41 (2.44%)
occurrences (all)	0	5	1
Rash macular			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Rash maculo-papular			
subjects affected / exposed	0 / 61 (0.00%)	12 / 130 (9.23%)	6 / 41 (14.63%)
occurrences (all)	0	12	6
Rash morbilliform			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Rash pruritic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rosacea			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	1	2	1

Scab			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Skin erosion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	1 / 61 (1.64%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	1	4	1
Skin fissures			
subjects affected / exposed	0 / 61 (0.00%)	17 / 130 (13.08%)	2 / 41 (4.88%)
occurrences (all)	0	17	2
Skin irritation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin mass			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Skin reaction			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Solar dermatitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Stasis dermatitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Swelling face			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Toxic skin eruption			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	0	4	1
Cystitis noninfective			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 61 (0.00%)	8 / 130 (6.15%)	1 / 41 (2.44%)
occurrences (all)	0	8	1
Haematuria			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Micturition urgency			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oliguria			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Proteinuria			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Renal injury			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Renal vein occlusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hyperthyroidism			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 61 (4.92%)	9 / 130 (6.92%)	7 / 41 (17.07%)
occurrences (all)	6	9	7
Arthritis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	3 / 61 (4.92%)	8 / 130 (6.15%)	8 / 41 (19.51%)
occurrences (all)	3	8	8
Bone pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Chondrocalcinosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Groin pain			

subjects affected / exposed	3 / 61 (4.92%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences (all)	3	3	1
Haemarthrosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Mobility decreased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	1	1	1
Muscle twitching			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 61 (1.64%)	8 / 130 (6.15%)	1 / 41 (2.44%)
occurrences (all)	1	8	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	1	1	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Musculoskeletal disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	2 / 61 (3.28%)	2 / 130 (1.54%)	4 / 41 (9.76%)
occurrences (all)	2	2	4
Musculoskeletal stiffness			

subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	4 / 61 (6.56%)	18 / 130 (13.85%)	4 / 41 (9.76%)
occurrences (all)	3	18	4
Neck mass			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	2 / 61 (3.28%)	5 / 130 (3.85%)	1 / 41 (2.44%)
occurrences (all)	2	5	1
Pain in extremity			
subjects affected / exposed	3 / 61 (4.92%)	9 / 130 (6.92%)	6 / 41 (14.63%)
occurrences (all)	3	9	6
Pain in jaw			
subjects affected / exposed	2 / 61 (3.28%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	2	1	0
Rhabdomyolysis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Spinal osteoarthritis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Spinal pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Tendonitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Trismus			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1

Abscess limb			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Acute sinusitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Acute tonsillitis			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	1 / 41 (2.44%)
occurrences (all)	0	3	1
Bacterial infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	2 / 41 (4.88%)
occurrences (all)	0	2	2
Cholangitis infective			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 61 (0.00%)	8 / 130 (6.15%)	0 / 41 (0.00%)
occurrences (all)	0	8	0
Conjunctivitis viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Enterobacter infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	1 / 61 (1.64%)	17 / 130 (13.08%)	7 / 41 (17.07%)
occurrences (all)	1	17	7

Erysipelas			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Fungal oesophagitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Helicobacter infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Herpes virus infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Impetigo			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Infected bites			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Influenza			
subjects affected / exposed	1 / 61 (1.64%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Klebsiella infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Lung infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Lymph gland infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 61 (4.92%)	8 / 130 (6.15%)	2 / 41 (4.88%)
occurrences (all)	3	8	2
Oral candidiasis			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	1 / 41 (2.44%)
occurrences (all)	0	5	1
Oral fungal infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Paronychia			
subjects affected / exposed	0 / 61 (0.00%)	9 / 130 (6.92%)	3 / 41 (7.32%)
occurrences (all)	0	9	3

Pharyngitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Pneumonia escherichia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pseudomonas infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Pulpitis dental			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	1 / 61 (1.64%)	16 / 130 (12.31%)	3 / 41 (7.32%)
occurrences (all)	1	16	3
Rhinitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	2 / 41 (4.88%)
occurrences (all)	1	1	2
Sinusitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Skin candida			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Skin infection			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	0	4	1
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Superinfection viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Tinea cruris			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Tinea pedis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Tinea versicolour			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Trichophytosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 61 (1.64%)	7 / 130 (5.38%)	0 / 41 (0.00%)
occurrences (all)	1	7	0
Vaginal infection			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 130 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Wound infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 130 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0

Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cell death			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	8 / 61 (13.11%)	22 / 130 (16.92%)	7 / 41 (17.07%)
occurrences (all)	8	22	7
Dehydration			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	1 / 41 (2.44%)
occurrences (all)	0	4	1
Diabetes mellitus			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Electrolyte imbalance			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Fluid retention			
subjects affected / exposed	0 / 61 (0.00%)	2 / 130 (1.54%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Gout			
subjects affected / exposed	1 / 61 (1.64%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Hyperamylasaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	0 / 41 (0.00%)
occurrences (all)	1	3	0
Hyperkalaemia			
subjects affected / exposed	0 / 61 (0.00%)	5 / 130 (3.85%)	0 / 41 (0.00%)
occurrences (all)	0	5	0
Hyperlipasaemia			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 61 (0.00%)	10 / 130 (7.69%)	2 / 41 (4.88%)
occurrences (all)	0	10	2
Hypocalcaemia			
subjects affected / exposed	0 / 61 (0.00%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Hypoglycaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	3 / 61 (4.92%)	13 / 130 (10.00%)	5 / 41 (12.20%)
occurrences (all)	3	13	5
Hypomagnesaemia			
subjects affected / exposed	0 / 61 (0.00%)	4 / 130 (3.08%)	3 / 41 (7.32%)
occurrences (all)	0	4	3
Hyponatraemia			
subjects affected / exposed	0 / 61 (0.00%)	7 / 130 (5.38%)	0 / 41 (0.00%)
occurrences (all)	0	7	0
Hypophosphataemia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 130 (2.31%)	2 / 41 (4.88%)
occurrences (all)	1	3	2
Hypoproteinaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Malnutrition			

subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Oligodipsia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 130 (0.77%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2012	1. Modified inclusion criterion to specify that subjects with locally advanced cutaneous melanoma must be unresectable in order to be considered eligible for the trial, and therefore patients with disease that may be cured by surgery were not eligible. 2. Modified exclusion criterion to define "clinically relevant impaired cardiovascular function" using standardized criteria. 3. Modified the wording of one of the censoring rules to account for the 12-week interval between tumor assessments after Cycle 13. 4. Clarified that the Cochran Mantel Haenszel (CMH) test was to be used for the analyses of ORR.
15 October 2012	1. Changed the definition of the sequence of treatment interruption, potential dose reduction or treatment discontinuation subsequent to detection of a Grade 3 or Grade 4 QTc prolongation. 2. Added that drugs known to prolong the QT interval were to be used with caution if they could not be avoided. 3. Corrected the duration of preservation of pharmacogenetic and biomarker samples. 4. Clarified that storage of dacarbazine is to be done according to the local Prescribing Information or Summary of Product Characteristics. 5. Clarified the follow-up for bone metastasis assessments. 6. Clarified pimasertib dispensation. 7. Corrected example of clinically relevant AEs.
05 June 2013	[16-12-2016 13:18] Uttam Singh: 1. Excluded subjects with elevated Creatine Phosphokinase (CPK) levels (> 2.5 × ULN) and/or a history of myositis or rhabdomyolysis. 2. Defined CPK Grade 2 or higher elevations as an Adverse Event of Special Interest. 3. Introduced procedures for appropriate management of elevated CPK levels. 4. Clarified that drugs considered being associated with muscle toxicity should be used with caution. 5. Clarified adequate contraceptive methods. 6. Defined acceptable time windows of trial treatment administration, visits and assessments. 7. Introduced administrative changes and correct typing errors and inconsistencies.
14 August 2014	1. Clarified and harmonize the inclusion/exclusion criteria for the global protocol. 2. Updated administrative sections of the protocol. 3. Provide an updated website path to provide information on medications that prolong the QT interval. 4. Correct grammatical and spelling errors. 5. Redefined the cut-off date for and the scope of the main analysis. 6. Allowed for the collection of imaging data in subjects who discontinued trial treatment without PD, death, or ICF withdrawal. 7. Added new sections for management of AEs. 8. Provided information to the Investigator on awareness of dehydration and renal failure and to accordingly update the Adverse Events of Special Interest section of the protocol. 9. Modified the expected trial duration and end of trial definition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Given the lack of impact on OS, single agent activity of pimasertib was deemed insufficient for full development. Therefore, pharmacokinetic and pharmacodynamics analyses were not performed as per change in planned analysis.

Notes: