

**Clinical trial results:****A Sequential Phase I study of MEK1/2 inhibitors PD-0325901 or Binimetinib combined with cMET inhibitor Crizotinib in RAS Mutant and RAS Wild Type(with aberrant c-MET) Colorectal Cancer Summary**

EudraCT number	2014-000463-40
Trial protocol	GB IE
Global end of trial date	03 December 2018

Results information

Result version number	v1 (current)
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information**Trial identification**

Sponsor protocol code	OCTO_049
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Additional study identifiers

ISRCTN number	ISRCTN18043777
ClinicalTrials.gov id (NCT number)	NCT02510001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington,n, Oxford, United Kingdom, OX3 7GB
Public contact	Mrs Jennifer Houlden, Oncology Clinical Trials Office, 44 01865227194, octo-mercuric@oncology.ox.ac.uk
Scientific contact	Mrs Jennifer Houlden, Oncology Clinical Trials Office, 44 01865227194, octo-mercuric@oncology.ox.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2018
Global end of trial reached?	Yes
Global end of trial date	03 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In the dose escalation part of the trial the main objective is to find the best doses for the combination of MEK inhibitors

PD-0325901 or Binimetinib with cMET inhibitor Crizotinib.

In the second (expansion) part of the trial we want to see how well this combination works in three particular sub-types

of bowel cancer. We want to do this by looking at tumour shrinkage, and at the molecular level through a variety of tests

on tumour and bloods samples.

Protection of trial subjects:

The Sponsor and Investigators ensured that this protocol was conducted in compliance with the European Clinical Trials Regulations, the Principles of Good Clinical Practice (GCP)³ and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

Following the end of study visit, patients will receive subsequent standard active, clinical trial, supportive and palliative care as appropriate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Ireland: 4
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	56
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initial escalation phase start Dec2014 over 4 sites, Oxford, Belfast, Belgium and Spain to Nov2015 .
Further escalation phase start Aug2016 over same sites plus Cardiff (activated Mar2017) to Jun2017.
Expansion phase start Oct2017 over same sites plus 2 sites in Paris, France and 1 site Dublin, Ireland.
Study recruitment end Oct2018.

Pre-assignment

Screening details:

Escalation phases 45/71 screened patients recruited.
Expansion phase 36/57 screened patients recruited to RAS MT CRC cohort; 1/4 patients RAS WT CRC.
Some patients declined due to 2 required tumour biopsies; RAS WT CRC cohort for eligibility biopsy availability.
Both phases most exclusions due to raised liver function, CK and albumin results.

Period 1

Period 1 title	Baseline (overall) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Dose escalation phase cohort 1 dose level 1
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	PD-0325901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

2mg BD Day 1-21 every 28 day cycle

Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

250mg OD Days 1-28 continuously

Arm title	Dose escalation phase cohort 2 dose level 2
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	PD-0325901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

2mg BD Day 1-21 every 28 day cycle

Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 250mg BD Days 1-28 continuously	
Arm title	Dose escalation phase cohort 3 dose level 3
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	PD-0325901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 4mg BD Day 1-21 every 28 day cycle	
Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 200mg BD Days 1-28 continuously	
Arm title	Dose escalation phase cohort 4 dose level 4
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	PD-0325901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 8mg BD Day 1-21 every 28 day cycle	
Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 200mg BD Days 1-28 continuously	
Arm title	Dose escalation phase cohort 7 dose level 5
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 200mg BD Days 1-28 continuously	

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 30mg BD continuously	
Arm title	Dose escalation phase cohort 12 dose level 5a
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 250mg OD Days 1-28 continuously	
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 30mg BD days 1-21 every 28 days	
Arm title	Dose escalation phase cohort 13 dose level 5 (interval dosing)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 200mg BD Days 1-28 continuously	
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 30mg BD continuously	
Arm title	Dose expansion phase
Arm description: Dosage determined following the recommended phase II dose identification in the dose escalation phase.	
Arm type	Experimental
Investigational medicinal product name	PF-02341066
Investigational medicinal product code	
Other name	Crizotinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

250mg OD Days 1-28 continuously

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30mg BD days 1-21 every 28 day cycle

Number of subjects in period 1	Dose escalation phase cohort 1 dose level 1	Dose escalation phase cohort 2 dose level 2	Dose escalation phase cohort 3 dose level 3
Started	6	5	6
Completed	6	5	6
Not completed	0	0	0
Physician decision	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Early disease progression	-	-	-

Number of subjects in period 1	Dose escalation phase cohort 4 dose level 4	Dose escalation phase cohort 7 dose level 5	Dose escalation phase cohort 12 dose level 5a
Started	8	8	7
Completed	6	4	5
Not completed	2	4	2
Physician decision	-	1	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	2	1
Early disease progression	1	1	1

Number of subjects in period 1	Dose escalation phase cohort 13 dose level 5 (interval dosing)	Dose expansion phase
Started	5	37
Completed	3	30
Not completed	2	7
Physician decision	-	-
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	5
Early disease progression	-	-

Baseline characteristics

Reporting groups

Reporting group title	Dose escalation phase cohort 1 dose level 1
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 2 dose level 2
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 3 dose level 3
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 4 dose level 4
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 7 dose level 5
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 12 dose level 5a
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 13 dose level 5 (interval dosing)
Reporting group description: -	
Reporting group title	Dose expansion phase
Reporting group description:	
Dosage determined following the recommended phase II dose identification in the dose escalation phase.	

Reporting group values	Dose escalation phase cohort 1 dose level 1	Dose escalation phase cohort 2 dose level 2	Dose escalation phase cohort 3 dose level 3
Number of subjects	6	5	6
Age categorical			
Units: Subjects			
Adults (18-64 years)	4	3	5
From 65-84 years	2	2	1
Age continuous			
Units: years			
median	65.8	64.8	58.4
full range (min-max)	36 to 78	48 to 69	52 to 71
Gender categorical			
Units: Subjects			
Female	4	3	5
Male	2	2	1

Reporting group values	Dose escalation phase cohort 4 dose level 4	Dose escalation phase cohort 7 dose level 5	Dose escalation phase cohort 12 dose level 5a
Number of subjects	8	8	7
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	6	5
From 65-84 years	3	2	2
Age continuous			
Units: years			
median	61.2	51	60
full range (min-max)	36 to 73	33 to 72	46 to 70

Gender categorical Units: Subjects			
Female	5	6	5
Male	3	2	2

Reporting group values	Dose escalation phase cohort 13 dose level 5 (interval dosing)	Dose expansion phase	Total
Number of subjects	5	37	82
Age categorical Units: Subjects			
Adults (18-64 years)	4	24	56
From 65-84 years	1	13	26
Age continuous Units: years			
median	55	62	
full range (min-max)	40 to 65	32 to 78	-
Gender categorical Units: Subjects			
Female	4	24	56
Male	1	13	26

End points

End points reporting groups

Reporting group title	Dose escalation phase cohort 1 dose level 1
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 2 dose level 2
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 3 dose level 3
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 4 dose level 4
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 7 dose level 5
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 12 dose level 5a
Reporting group description: -	
Reporting group title	Dose escalation phase cohort 13 dose level 5 (interval dosing)
Reporting group description: -	
Reporting group title	Dose expansion phase
Reporting group description: Dosage determined following the recommended phase II dose identification in the dose escalation phase.	
Subject analysis set title	Dose Escalation Phase Binimetinib/PF-02341066
Subject analysis set type	Intention-to-treat
Subject analysis set description: Second dose escalation phase - cohorts 7, 12 and 13	
Subject analysis set title	Dose expansion phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Dose expansion phase all patients	

Primary: Maximal Tolerated Dose (MTD) of PD-0325901 and PF-02341066

End point title	Maximal Tolerated Dose (MTD) of PD-0325901 and PF-02341066 ^{[1][2]}
End point description: Determine maximum tolerated dose (MTD) of PD-0325901 with Crizotinib (PF-02341066) according to toxicities graded by NCI CTCAE v4.03, in patients with advanced solid tumours. MTD for the PDB 0325901/ PF-02341066 combination was 8mg BD(days1-21) and 200mg BD continuously in a 28 day cycle.	
End point type	Primary
End point timeframe: Dose Escalation Phase: treatment Cycle 1 28 days (plus 7 day run-in for PD0325901/PF-02341066 combination)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The outcome is just number of DLTs occurring, there is no statistical analysis necessary.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There are three different phases in the trial (two dose escalation phases, with different drugs, and one dose expansion phase), and each phase has a different primary outcome.

End point values	Dose escalation phase cohort 1 dose level 1	Dose escalation phase cohort 2 dose level 2	Dose escalation phase cohort 3 dose level 3	Dose escalation phase cohort 4 dose level 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	6
Units: Dose Limiting Toxicities (DLTs)	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Maximal Tolerated Dose (MTD) of PD-Binimetinib and PF-02341066

End point title	Maximal Tolerated Dose (MTD) of PD-Binimetinib and PF-02341066 ^{[3][4]}
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End point description:

To determine the maximal tolerated dose (MTD) of Binimetinib with PF-02341066 according to toxicities graded by NCI CTCAE V4.03 in cycle 1 of treatment. Binimetinib 30mg BD on days 1 - 21 every 28 days with Crizotinib 250 mg OD continuously is the recommended dose and schedule for further evaluation in our and other trials.

End point type	Primary
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End point timeframe:

Dose Escalation Phase: treatment Cycle 1 - 28 days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The outcome is just number of DLTs occurring, there is no statistical analysis necessary.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There are three different phases in the trial (two dose escalation phases, with different drugs, and one dose expansion phase), and each phase has a different primary outcome.

End point values	Dose escalation phase cohort 7 dose level 5	Dose escalation phase cohort 12 dose level 5a	Dose escalation phase cohort 13 dose level 5 (interval dosing)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	5	
Units: Dose Limiting Toxicities (DLTs)	2	2	1	

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Response to Binimetinib Combined With PF-02341066

End point title	Clinical Response to Binimetinib Combined With PF-
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End point description:

To investigate best response to treatment with RPII dose of Binimetinib with Crizotinib (PF-02341066), in patients with a) RASMT CRC or b) RASWT/cMET mut amplified CRC or c) RASWT/c-MET over-expressed CRC, as defined by stable, partially or completely responding disease using RECIST version 1.1.

End point type	Primary
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End point timeframe:

Dose Expansion phase: change from baseline and up to 12 months.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The outcome is just the number of patients experiencing each response category, there is no statistical analysis necessary.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There are three different phases in the trial (two dose escalation phases, with different drugs, and one dose expansion phase), and each phase has different outcomes.

End point values	Dose expansion phase			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Participants				
Stable Disease	7			
Progressive Disease	22			
Early death from malignant disease	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival ^[7]
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End point description:

End point type	Secondary
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End point timeframe:

Length of study

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There are three different phases in the trial (two dose escalation phases, with different drugs, and one dose expansion phase), and each phase has different outcomes.

End point values	Dose expansion phase	Dose Escalation Phase Binimetinib/PF-02341066		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	36	20		
Units: Months				
median (confidence interval 95%)	1.81 (1.51 to 2.04)	2.66 (1.81 to 5.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title Overall survival^[8]

End point description:

End point type Secondary

End point timeframe:

Length of study

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There are three different phases in the trial (two dose escalation phases, with different drugs, and one dose expansion phase), and each phase has different outcomes.

End point values	Dose expansion phase	Dose Escalation Phase Binimetinib/PF-02341066		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	36	20		
Units: months				
median (confidence interval 95%)	5.62 (2.79 to 7.40)	8.22 (3.95 to 100000)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring starts from the time the patient consents to the study until they complete the trial

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Dose escalation phase 1 - PF-02341066 and PD-0325901
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Reporting group description:

Cohorts 1, 2, 3, 4

Reporting group title	Dose escalation phase 2 - PF-02341066 and Binimetinib
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Reporting group description:

Cohorts 7, 12, 13

Reporting group title	Dose expansion phase - PF-02341066 and Binimetinib
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Reporting group description: -

Serious adverse events	Dose escalation phase 1 - PF-02341066 and PD-0325901	Dose escalation phase 2 - PF-02341066 and Binimetinib	Dose expansion phase - PF-02341066 and Binimetinib
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)	12 / 20 (60.00%)	18 / 37 (48.65%)
number of deaths (all causes)	18	15	27
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain metastases			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Postural hypotension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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
Pulmonary embolism			

subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thromboembolic event			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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
General disorders and administration site conditions			
Edema face			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscositis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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			
Ejection fraction decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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			
Postoperative haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Tingling in lower limbs			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Central serous retinopathy (Bilateral)			

subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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
Bowel obstruction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (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
Colonic obstruction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (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 / 25 (0.00%)	1 / 20 (5.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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 gastrointestinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Hypertransaminasaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (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
Worsening back pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
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			
Abdominal infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (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
Lung infection			
subjects affected / exposed	0 / 25 (0.00%)	3 / 20 (15.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (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
Wound infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (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
Metabolism and nutrition disorders			
Cytolysis			

subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dose escalation phase 1 - PF-02341066 and PD-0325901	Dose escalation phase 2 - PF-02341066 and Binimetinib	Dose expansion phase - PF-02341066 and Binimetinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	20 / 20 (100.00%)	37 / 37 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Hypotension			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	2 / 37 (5.41%) 2
Lymphoedema subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 5	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Postural hypotension subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 2
Thrombosis subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Surgical and medical procedures Cataract operation subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	6 / 20 (30.00%) 10	9 / 37 (24.32%) 12
Chest pain subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 2	0 / 37 (0.00%) 0
Chills subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Edema subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Edema face subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Edema limbs subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Edema lower limb			

subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Edema extremities			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Edema of legs			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	10 / 25 (40.00%)	10 / 20 (50.00%)	14 / 37 (37.84%)
occurrences (all)	18	16	30
Fever			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	4 / 37 (10.81%)
occurrences (all)	2	1	5
Flu like symptoms			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Foot oedema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Generalised oedema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Hand swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Leg oedema			
subjects affected / exposed	2 / 25 (8.00%)	2 / 20 (10.00%)	0 / 37 (0.00%)
occurrences (all)	2	3	0
Malaise			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Mucositis			

subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	1 / 37 (2.70%)
occurrences (all)	2	1	2
Oedema			
subjects affected / exposed	1 / 25 (4.00%)	2 / 20 (10.00%)	1 / 37 (2.70%)
occurrences (all)	4	4	1
Oedema abdomen			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Oedema arms			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Oedema extremities			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Oedema of lower extremities			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	1 / 37 (2.70%)
occurrences (all)	1	1	1
Orafacial oedema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Peripheral oedema			
subjects affected / exposed	0 / 25 (0.00%)	2 / 20 (10.00%)	0 / 37 (0.00%)
occurrences (all)	0	4	0
Retrosternal chest pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Rigors			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Serous discharge			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Swelling of legs			

subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Teeth chattering subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4	6 / 20 (30.00%) 9	5 / 37 (13.51%) 8
Dysphonia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	1 / 20 (5.00%) 1	5 / 37 (13.51%) 8
Epistaxis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Exertional dyspnoea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	2 / 37 (5.41%) 2
Hoarseness subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 2	0 / 37 (0.00%) 0
Pleural effusion subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 20 (10.00%) 3	0 / 37 (0.00%) 0
Pleurisy subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Pneumothorax subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Productive cough			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 20 (10.00%) 2	0 / 37 (0.00%) 0
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Respiratory distress subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Rib pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Shortness of breath subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	2 / 37 (5.41%) 2
Sore throat subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 20 (10.00%) 2	0 / 37 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	1 / 37 (2.70%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	2 / 37 (5.41%) 2
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Confusional state subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Depressed mood subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Insomnia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1

Libido decreased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Low mood subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 5	3 / 20 (15.00%) 4	8 / 37 (21.62%) 17
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4	3 / 20 (15.00%) 5	9 / 37 (24.32%) 13
Blood albumin decreased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 2
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 7	0 / 20 (0.00%) 0	6 / 37 (16.22%) 9
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	7 / 20 (35.00%) 19	11 / 37 (29.73%) 25
Blood creatine increased subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Blood potassium decreased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 20 (10.00%) 2	0 / 37 (0.00%) 0
Blood pressure increased			

subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Blood sodium decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Body temperature increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Electrocardiogram Qtc Interval Prolonged			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	2
Ggt increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Glucose increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Ldh increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Left ventricular ejection fraction decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Platelet count decreased			

subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	2 / 37 (5.41%)
occurrences (all)	1	1	2
Protein total decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Qt prolonged			
subjects affected / exposed	4 / 25 (16.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	4	0	0
Sodium decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	1	4	0
Transaminitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Troponin increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	2
Weight gain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Weight loss			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Intestinal stoma Complication			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Prolapse of intestinal stoma			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Scar subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Stoma site bleeding subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Vascular access complication subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Wound pain subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
K+ decreased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 2	0 / 37 (0.00%) 0
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Extrasystoles subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Aphasia			

subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	4 / 20 (20.00%)	2 / 37 (5.41%)
occurrences (all)	1	5	3
Dizziness postural			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Expressive dysphasia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Localised numbness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Neuropathic pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Neuropathy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Neuropathy peripheral			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Neurotoxicity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	3	1	0
Paraesthesia Lower limb			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 20 (15.00%) 3	0 / 37 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	2 / 37 (5.41%) 4
Tremor subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Vasovagal attack subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Visual field defect subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Weakness left or right side subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 9	1 / 20 (5.00%) 1	9 / 37 (24.32%) 16
Neutropenia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Ear and labyrinth disorders			
Ear disorder subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Eye disorders			

Blepharitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Chorioretinopathy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Conjunctival haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Corneal opacity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Eye disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Eyelid function disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Periorbital oedema			
subjects affected / exposed	0 / 25 (0.00%)	3 / 20 (15.00%)	1 / 37 (2.70%)
occurrences (all)	0	3	1
Photophobia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	2
Retinal detachment			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Retinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Subconjunctival haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0

Vision abnormal subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 2	0 / 37 (0.00%) 0
Visual disturbance subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Abdominal pain subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	1 / 20 (5.00%) 3	5 / 37 (13.51%) 7
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Ascites subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 20 (5.00%) 6	0 / 37 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	12 / 25 (48.00%) 20	4 / 20 (20.00%) 5	9 / 37 (24.32%) 12
Diarrhoea subjects affected / exposed occurrences (all)	10 / 25 (40.00%) 15	14 / 20 (70.00%) 28	18 / 37 (48.65%) 29
Dyspepsia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 20 (5.00%) 1	1 / 37 (2.70%) 1
Dry mouth subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 20 (5.00%) 1	1 / 37 (2.70%) 1
Epigastric pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Frequent bowel movements			

subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Haemorrhoids			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Heartburn			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Intestinal obstruction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Loose stools			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	11 / 25 (44.00%)	11 / 20 (55.00%)	20 / 37 (54.05%)
occurrences (all)	20	16	29
Nausea and vomiting			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Postprandial Emesis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Rectal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Right upper quadrant pain			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Sore gums subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Stomach cramps subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Stomach pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Stomatitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	10 / 25 (40.00%) 20	6 / 20 (30.00%) 9	19 / 37 (51.35%) 37
Swelling of hands subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Hepatobiliary disorders Hepatic haemorrhage subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Hypertransaminaemia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 2
Liver pain subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 20 (10.00%) 2	1 / 37 (2.70%) 1
Skin and subcutaneous tissue disorders Alopecia			

subjects affected / exposed	1 / 25 (4.00%)	2 / 20 (10.00%)	0 / 37 (0.00%)
occurrences (all)	1	2	0
Dermatitis acneiform			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	3 / 37 (8.11%)
occurrences (all)	2	1	3
Facial rash			
subjects affected / exposed	3 / 25 (12.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Genital itching			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Itchy scalp			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Macular rash			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Maculopapular rash			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Neck rash			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	3 / 37 (8.11%)
occurrences (all)	1	0	3
Papular rash			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	5 / 37 (13.51%)
occurrences (all)	0	0	6
Rash			

subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 8	7 / 20 (35.00%) 12	11 / 37 (29.73%) 21
Rash acneiform subjects affected / exposed occurrences (all)	9 / 25 (36.00%) 12	8 / 20 (40.00%) 12	13 / 37 (35.14%) 19
Rash face subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 20 (10.00%) 2	1 / 37 (2.70%) 1
Rosacea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Skin oedema subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Skin peeling subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Skin rash subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 20 (15.00%) 5	0 / 37 (0.00%) 0
Skin toxicity subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	2 / 37 (5.41%) 4
Rash on Legs and Arms subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0

Renal impairment			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Urinary frequency			
subjects affected / exposed	12 / 25 (48.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Urine incontinence			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	3 / 37 (8.11%)
occurrences (all)	0	5	4
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	2	0	4
Finger cramps			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Hypokalaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Intercostal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Joint instability			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Muscle ache			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Myalgia			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 20 (15.00%) 3	1 / 37 (2.70%) 1
Myalgia of lower extremities subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Neck pain subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Osteoarticular pain subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0
Osteonecrosis of jaw subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Pain in hip subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 3	0 / 37 (0.00%) 0
Pain in jaw subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 3	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Painful hips subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Shoulder pain subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Infections and infestations			
Abdominal abscess subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Candida infection subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Device related infection subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 37 (0.00%) 0

Ear infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Furunculosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Herpes lesion Intra-Oral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Intra-abdominal abscess			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Oral candida			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Parotiditis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Periorbital infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Pustular rash			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 20 (5.00%) 1	1 / 37 (2.70%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	2 / 37 (5.41%) 3
Wound infection subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Decreased appetite subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Dehydration subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 37 (2.70%) 1
Gout subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	1 / 37 (2.70%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	1 / 37 (2.70%) 1
Hypoalbuminaemia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 10	3 / 20 (15.00%) 4	3 / 37 (8.11%) 5
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	0 / 20 (0.00%) 0	0 / 37 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2014	In response to MHRA Notice For Grounds for Non Acceptance: clarification re maximum tolerated dose (MTD) and dose modification; Protocol and Patient Information Sheet (PIS) inclusion of MHRA contraception guidelines; IMP information correction to Clinical Trial Application (CTA).
04 February 2015	Amend IRAS Dataset updated with changes and changes to trial documents: Protocol; Dose Escalation and Dose Expansion PIS and Consent forms (CFs); Patient Diary Card; Patient Study Card Belfast site Principal Investigator (PI) - notice of change of status. Patient types changes from KRASMT AND KRASWT to RASMT AND RASWT - biomarker studies shown NRASMT colorectal cancer (CRC) behaves in similar way to KRASMT CRC so RAS categorisation prevents exclusion of eligible patients. Patient number clarification as 12 per cohort. Change to laboratory information for sample transfer and corrections to sample collection timepoints. Additional information for PIS on potential side effects as PPI request. Study schedule changes for feasibility purposes. Management of dosing change from drugs being taken separately to same time for patient tolerability and ease as according to pharmacological company guidance. Dose modification clarifications and amendment of contraception section according to MHRA update guidelines. IRAS dataset changes for additional information on collaborating laboratories, radiation information and optional CT guided biopsy clarifications in line with radiation risk assessment, participating site information corrected as one site previously not included plus other minor administrative changes.
21 July 2015	Protocol amendment for Inclusion of interim dose level schedule as considered likely that highest dose level would not be tolerated and sound scientific rationale that PD-0325901 treatment would be tolerated at a higher than 4mg dose but less than the higher 8mg dose currently scheduled according to emergent clinical data and dose limiting toxicities. Additional exclusion criteria further to clinical decision to avoid recruiting patients who had pre-study hypoalbuminaemia or had required multiple ascites or pleural taps as the first 3 recruited trial patients experienced hypoalbuminaemia at Grade 1 and 2. Removal of Ondansetron from Protocol as recommended treatment for nausea and vomiting as the drug has confirmed risk of QT prolongation which is a trial exclusion criteria. Correction to omission in IRAS dataset, Protocol schedule of events table, Dose Escalation and Dose Expansion phase PIS for ECG event Cycle 1 Day 15 in line with schedule of assessments text. Protocol footnotes for dose escalation and expansion phases schedule of events tables changes to remove time window for PBMC samples as inappropriate to the requirement of the protocol sample collection times.

06 May 2016	<p>Replacement of study drug MEK inhibitor Pfizer's PD-0325901 for Array Biopharma's Binimetinib to be combined with the same Pfizer MET inhibitor PF-02341066 (Crizotinib) which also included change to study title on all study documentation to reflect the inclusion of two different MEK inhibitors used in the trial. This change was due to Pfizer's internal decision to discontinue PD-0325901 development therefore creating an issue of drug security for the remainder of this trial and Binimetinib was chosen due to availability of sound data on the drug and its considered suitability as a combination therapy with Pfizer's PF-02341066. A further short 3 dose escalation phase was therefore required to assess safety and tolerability and to determine the recommended dose for the dose expansion phase of the trial.</p> <p>Change to protocol and patient documents for the study design of the dose expansion phase to incorporate specific cohorts of RAS wild type colorectal patients and the greater patient recruitment target to include specific RAS Wild type c_MET high, super and amplified colorectal cancer patient groups. This change was made from experience gained on relevant Phase III studies which led the consortium members to consider that it is beneficial to study the effect of the combined treatment on these patients due to their dependency on c_MET, and who are therefore most likely to benefit from such treatment. It was also to provide a clear positive signal for the next protocol phase and so provide credence to the rationale for Protocol 2. this also led to changes to the sample collection timepoints and study schedule in line with the changed drug dosing regimen. Binimetinib Investigator Brochure, and protocol and patient documents included Array dose modification and safety information.</p> <p>Notification of change of investigator at an existing site: formerly Prof Pierre Laurent-Puig at the European St Georges Pompidou Hospital, Paris, to Dr Geraldine Perkins.</p>
28 March 2017	<p>Protocol change to dose limiting (DLT) criteria and change to IMP dose modifications classified as grade 3 and 4 specifically for creatinine kinase (CK) elevation following information provided by Array Biopharma (provider of Binimetinib IMP) which has been reviewed and approved by the FDA.</p>
20 June 2017	<p>Amendment to protocol and patient documentation for the change to study design of the dose expansion phase to incorporate a two-staged review design using a greater number of patients for each of the three specific cohorts of RAS mutant and RAS wild type c-MET aberrant colorectal cancer patients. Further information from relevant phase III studies led to the MeRCuRIC consortium's decision to expand the RASWT/cMET group so the effect of the combined treatment could be evaluated in c-MET high expressors as well as c-MET superexpressor groups and potentially a c-MET amplified cohort. The c-MET high expressor and amplified patient groups are the most likely patients with dependency on c-MET who would benefit from treatment and be more likely to provide a clear positive signal and information for patient selection in the phase II trial.</p> <p>Update to eligibility criteria to include prior treatment with an EGFR target monoclonal antibody and contraception guidelines</p> <p>Update to the dose modification guidelines for current information for pneumonitis and left ventricular systolic dysfunctions.</p> <p>Update to number of participating sites (4 to 5) in the dose escalation phase to aid recruitment as well as to the potential number (8 to 10) for the dose expansion phase supporting recruitment to the rarer groups of colorectal cancer patients. Patient numbers amended for escalation phase from 24 to 25 reflecting the numbers actually required for exploring tolerability of the IMP combination at intermediate dose levels previously not anticipated.</p> <p>Change to the dose expansion phase sample collection profile for pharmacodynamics samples, removing the pERK analysis of PBMC samples in blood. Skin biopsies are also reduced to be only performed on the first 10 patients enrolled to the dose expansion phase.</p> <p>Update/clarification of Dose Expansion Schedule changes for clarification of post end of treatment and follow up.</p>

04 October 2018	<p>Update to Protocol and CTA to include new laboratory details for processing of screening tumour samples for evaluation of RAS Wild Type CRC c-MET expression and amplification. the assay required for completion of evaluation processes as needed for the genotyping for the protocol was no longer available at the designated QUB molecular pathology laboratory in Belfast. The new central laboratory facility has been included to perform these required procedures under the directorship of the Paris Descartes University molecular laboratory (PDUM). A new material transfer agreement was also completed for transfer of the extracted DNA samples to this laboratory.</p> <p>Update to Screening Patient Information Sheet for tumour test reporting clarification as the transfer to the new laboratory facility required a potentially longer reporting time from within 7-14 days to being available from 7-14 days. This amendment did not halt the progress of trial as sites were able to continue to recruit patients to the RAS Mutant CRC cohort, however it did cause delays to the recruitment for the RAS Wild Type CRC cohorts.</p>
26 November 2018	<p>Change to protocol synopsis for information on early closure of recruitment to the trial as closed 23Oct2018 with 82 patients recruited. This was following significant difficulties encountered in recruiting to the dose expansion phase RAS WT CRC patient cohorts within the constraints of the EU grant supporting the trial. The decision was made by the Trial Management Group with the support of the FP7 consortium members and trial sponsor.</p> <p>Clarifications were also made to the binimetinib dose modification for creatinine kinase in line with Array biopharma FDA approved guidelines as inconsistencies were noted between 2 sections of the protocol.</p>

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.

<p>Following regulatory approval for recruitment to the RAS Wild Type CRC patient cohorts there was evidential lack of feasibility for recruiting to the rarer RAS wild type CRC cohorts within the remaining funding period.</p>

Notes: