



## 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 |
|-----------------------|----------|

##### 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)<sup>3</sup> 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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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 |
|------------------------------|-----|

|                  |   |
|------------------|---|
| <b>Arm title</b> | Dose escalation phase cohort 1 dose level 1 |
|------------------|---|

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

|                  |   |
|------------------|---|
| <b>Arm title</b> | Dose escalation phase cohort 2 dose level 2 |
|------------------|---|

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:<br>250mg BD Days 1-28 continuously    |   |
| <b>Arm title</b>   | 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:<br>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:<br>200mg BD Days 1-28 continuously    |   |
| <b>Arm title</b>   | 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:<br>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:<br>200mg BD Days 1-28 continuously    |   |
| <b>Arm title</b>   | 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:<br>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:<br>30mg BD continuously   |  |
| <b>Arm title</b>   | 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:<br>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:<br>30mg BD days 1-21 every 28 days                                  |  |
| <b>Arm title</b>   | 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:<br>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:<br>30mg BD continuously   |  |
| <b>Arm title</b>   | 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<br>Units: Subjects    |   |   |   |
| Adults (18-64 years)                  | 4   | 3   | 5   |
| From 65-84 years                      | 2   | 2   | 1   |
| Age continuous<br>Units: years        |   |   |   |
| median                                | 65.8  | 64.8  | 58.4  |
| full range (min-max)                  | 36 to 78                                    | 48 to 69                                    | 52 to 71                                    |
| Gender categorical<br>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<br>Units: Subjects |   |   |   |
| Adults (18-64 years)               | 5   | 6   | 5   |
| From 65-84 years                   | 3   | 2   | 2   |
| Age continuous<br>Units: years     |   |   |   |
| median                             | 61.2  | 51  | 60  |
| full range (min-max)               | 36 to 73                                    | 33 to 72                                    | 46 to 70                                      |

|                                       |   |   |   |
|---------------------------------------|---|---|---|
| Gender categorical<br>Units: Subjects |   |   |   |
| Female                                | 5 | 6 | 5 |
| Male                                  | 3 | 2 | 2 |

| <b>Reporting group values</b>         | Dose escalation<br>phase cohort 13<br>dose level 5<br>(interval dosing) | Dose expansion<br>phase | Total |
|---------------------------------------|---|-------------------------|-------|
| Number of subjects                    | 5   | 37                      | 82    |
| Age categorical<br>Units: Subjects    |   |                         |       |
| Adults (18-64 years)                  | 4   | 24                      | 56    |
| From 65-84 years                      | 1   | 13                      | 26    |
| Age continuous<br>Units: years        |   |                         |       |
| median                                | 55  | 62                      |       |
| full range (min-max)                  | 40 to 65  | 32 to 78                | -     |
| Gender categorical<br>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:<br>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:<br>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:<br>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 <sup>[1][2]</sup> |
| End point description:<br>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.<br><br>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:<br>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 <sup>[3]</sup> <sup>[4]</sup> |
|-----------------|--|

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 |
|----------------|---------|

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- |
|-----------------|--|

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 |
|----------------|---------|

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 <sup>[7]</sup> |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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<br>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 <sup>[8]</sup> |
|-----------------|---------------------------------|

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<br>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 |
|-----------------|------------|

### Dictionary used

|                 |           |
|-----------------|-----------|
| Dictionary name | NCI CTCAE |
|-----------------|-----------|

|                    |      |
|--------------------|------|
| Dictionary version | 4.03 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Cohorts 1, 2, 3, 4

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

Reporting group description:

Cohorts 7, 12, 13

|                       |  |
|-----------------------|--|
| Reporting group title | Dose expansion phase - PF-02341066 and Binimetinib |
|-----------------------|--|

Reporting group description: -

| <b>Serious adverse events</b>                                       | 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          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| <b>Abdominal pain</b>                           |                |                |                |
| 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          |
| <b>Ascites</b>                                  |                |                |                |
| 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          |
| <b>Bowel obstruction</b>                        |                |                |                |
| 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          |
| <b>Colonic obstruction</b>                      |                |                |                |
| 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          |
| <b>Constipation</b>                             |                |                |                |
| 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          |
| <b>Diarrhoea</b>                                |                |                |                |
| 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          |
| <b>Lower gastrointestinal haemorrhage</b>       |                |                |                |
| 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          |
| <b>Hepatobiliary disorders</b>                  |                |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| 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 %

| <b>Non-serious adverse events</b>                     | 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                          | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 2 / 37 (5.41%)  |
| occurrences (all)                                    | 0              | 0               | 2               |
| Lymphoedema  |                |                 |                 |
| subjects affected / exposed                          | 1 / 25 (4.00%) | 0 / 20 (0.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                                    | 5              | 0               | 0               |
| Postural hypotension                                 |                |                 |                 |
| subjects affected / exposed                          | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                                    | 0              | 0               | 2               |
| Thrombosis   |                |                 |                 |
| subjects affected / exposed                          | 0 / 25 (0.00%) | 1 / 20 (5.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                                    | 0              | 1               | 0               |
| Surgical and medical procedures                      |                |                 |                 |
| Cataract operation                                   |                |                 |                 |
| subjects affected / exposed                          | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                                    | 0              | 0               | 1               |
| General disorders and administration site conditions |                |                 |                 |
| Asthenia   |                |                 |                 |
| subjects affected / exposed                          | 2 / 25 (8.00%) | 6 / 20 (30.00%) | 9 / 37 (24.32%) |
| occurrences (all)                                    | 2              | 10              | 12              |
| Chest pain   |                |                 |                 |
| subjects affected / exposed                          | 0 / 25 (0.00%) | 1 / 20 (5.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                                    | 0              | 2               | 0               |
| Chills   |                |                 |                 |
| subjects affected / exposed                          | 2 / 25 (8.00%) | 1 / 20 (5.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                                    | 2              | 1               | 0               |
| Edema  |                |                 |                 |
| subjects affected / exposed                          | 1 / 25 (4.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                                    | 1              | 0               | 1               |
| Edema face   |                |                 |                 |
| subjects affected / exposed                          | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                                    | 0              | 0               | 1               |
| Edema limbs  |                |                 |                 |
| subjects affected / exposed                          | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                                    | 0              | 0               | 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              |
| Orfacial 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<br>occurrences (all)   | 1 / 25 (4.00%)<br>1  | 1 / 20 (5.00%)<br>1  | 0 / 37 (0.00%)<br>0  |
| Teeth chattering<br>subjects affected / exposed<br>occurrences (all)   | 1 / 25 (4.00%)<br>1  | 0 / 20 (0.00%)<br>0  | 0 / 37 (0.00%)<br>0  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)              | 0 / 25 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1  | 0 / 37 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 3 / 25 (12.00%)<br>4 | 6 / 20 (30.00%)<br>9 | 5 / 37 (13.51%)<br>8 |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 25 (4.00%)<br>2  | 1 / 20 (5.00%)<br>1  | 5 / 37 (13.51%)<br>8 |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 25 (4.00%)<br>1  | 0 / 20 (0.00%)<br>0  | 0 / 37 (0.00%)<br>0  |
| Exertional dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  | 2 / 37 (5.41%)<br>2  |
| Hoarseness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0  | 1 / 20 (5.00%)<br>2  | 0 / 37 (0.00%)<br>0  |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0  | 2 / 20 (10.00%)<br>3 | 0 / 37 (0.00%)<br>0  |
| Pleurisy<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  | 1 / 37 (2.70%)<br>1  |
| Pneumothorax<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  | 1 / 37 (2.70%)<br>1  |
| Productive cough   |                      |                      |                      |



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

|  |                      |                       |                        |
|--|----------------------|-----------------------|------------------------|
| Libido decreased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0   | 1 / 37 (2.70%)<br>1    |
| Low mood<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0   | 1 / 37 (2.70%)<br>1    |
| Investigations   |                      |                       |                        |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 3 / 25 (12.00%)<br>5 | 3 / 20 (15.00%)<br>4  | 8 / 37 (21.62%)<br>17  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 3 / 25 (12.00%)<br>4 | 3 / 20 (15.00%)<br>5  | 9 / 37 (24.32%)<br>13  |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)                | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0   | 1 / 37 (2.70%)<br>2    |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)   | 5 / 25 (20.00%)<br>7 | 0 / 20 (0.00%)<br>0   | 6 / 37 (16.22%)<br>9   |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0  | 7 / 20 (35.00%)<br>19 | 11 / 37 (29.73%)<br>25 |
| Blood creatine increased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 25 (4.00%)<br>1  | 0 / 20 (0.00%)<br>0   | 1 / 37 (2.70%)<br>1    |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)                | 0 / 25 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0   | 1 / 37 (2.70%)<br>1    |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 25 (4.00%)<br>1  | 0 / 20 (0.00%)<br>0   | 1 / 37 (2.70%)<br>1    |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 25 (0.00%)<br>0  | 2 / 20 (10.00%)<br>2  | 0 / 37 (0.00%)<br>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  | 0 / 25 (0.00%) | 0 / 20 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0              | 1              |
| Scar                         |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0              | 1              |
| Stoma site bleeding          |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0              | 1              |
| Vascular access complication |                |                |                |
| subjects affected / exposed  | 1 / 25 (4.00%) | 0 / 20 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Wound pain                   |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0              | 1              |
| K+ decreased                 |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%) | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 2              | 0              |
| Cardiac disorders            |                |                |                |
| Bradycardia                  |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%) | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Extrasystoles                |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%) | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Pericardial effusion         |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%) | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Sinus bradycardia            |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0              | 1              |
| Nervous system disorders     |                |                |                |
| Amnesia                      |                |                |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%) | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 1              | 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          | 0 / 25 (0.00%)  | 3 / 20 (15.00%) | 0 / 37 (0.00%)  |
| occurrences (all)                    | 0               | 3               | 0               |
| Presyncope                           |                 |                 |                 |
| subjects affected / exposed          | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 2 / 37 (5.41%)  |
| occurrences (all)                    | 0               | 1               | 4               |
| Tremor                               |                 |                 |                 |
| subjects affected / exposed          | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0               |
| Vasovagal attack                     |                 |                 |                 |
| subjects affected / exposed          | 2 / 25 (8.00%)  | 0 / 20 (0.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                    | 2               | 0               | 0               |
| Visual field defect                  |                 |                 |                 |
| subjects affected / exposed          | 1 / 25 (4.00%)  | 0 / 20 (0.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Weakness left or right side          |                 |                 |                 |
| subjects affected / exposed          | 1 / 25 (4.00%)  | 0 / 20 (0.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                    | 2               | 0               | 0               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 7 / 25 (28.00%) | 1 / 20 (5.00%)  | 9 / 37 (24.32%) |
| occurrences (all)                    | 9               | 1               | 16              |
| Neutropenia                          |                 |                 |                 |
| subjects affected / exposed          | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0               |
| Thrombocytopenia                     |                 |                 |                 |
| subjects affected / exposed          | 0 / 25 (0.00%)  | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                    | 0               | 0               | 1               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Ear disorder                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 0 / 37 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0               |
| Vertigo                              |                 |                 |                 |
| subjects affected / exposed          | 0 / 25 (0.00%)  | 0 / 20 (0.00%)  | 1 / 37 (2.70%)  |
| occurrences (all)                    | 0               | 0               | 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<br>subjects affected / exposed<br>occurrences (all)      | 0 / 25 (0.00%)<br>0    | 1 / 20 (5.00%)<br>2    | 0 / 37 (0.00%)<br>0    |
| Visual disturbance<br>subjects affected / exposed<br>occurrences (all)   | 3 / 25 (12.00%)<br>3   | 0 / 20 (0.00%)<br>0    | 0 / 37 (0.00%)<br>0    |
| Gastrointestinal disorders   |                        |                        |                        |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0    | 0 / 20 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1    |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 3 / 25 (12.00%)<br>3   | 1 / 20 (5.00%)<br>3    | 5 / 37 (13.51%)<br>7   |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0    | 0 / 20 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1    |
| Ascites<br>subjects affected / exposed<br>occurrences (all)              | 1 / 25 (4.00%)<br>1    | 1 / 20 (5.00%)<br>6    | 0 / 37 (0.00%)<br>0    |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 12 / 25 (48.00%)<br>20 | 4 / 20 (20.00%)<br>5   | 9 / 37 (24.32%)<br>12  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 10 / 25 (40.00%)<br>15 | 14 / 20 (70.00%)<br>28 | 18 / 37 (48.65%)<br>29 |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 25 (8.00%)<br>2    | 1 / 20 (5.00%)<br>1    | 1 / 37 (2.70%)<br>1    |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)            | 2 / 25 (8.00%)<br>2    | 1 / 20 (5.00%)<br>1    | 1 / 37 (2.70%)<br>1    |
| Epigastric pain<br>subjects affected / exposed<br>occurrences (all)      | 1 / 25 (4.00%)<br>1    | 1 / 20 (5.00%)<br>1    | 0 / 37 (0.00%)<br>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            | 0 / 25 (0.00%)   | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)                      | 0                | 0               | 1                |
| Sore gums                              |                  |                 |                  |
| subjects affected / exposed            | 2 / 25 (8.00%)   | 0 / 20 (0.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)                      | 2                | 0               | 0                |
| Stomach cramps                         |                  |                 |                  |
| subjects affected / exposed            | 0 / 25 (0.00%)   | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)                      | 0                | 0               | 1                |
| Stomach pain                           |                  |                 |                  |
| subjects affected / exposed            | 1 / 25 (4.00%)   | 0 / 20 (0.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)                      | 2                | 0               | 0                |
| Stomatitis                             |                  |                 |                  |
| subjects affected / exposed            | 1 / 25 (4.00%)   | 0 / 20 (0.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)                      | 1                | 0               | 0                |
| Vomiting                               |                  |                 |                  |
| subjects affected / exposed            | 10 / 25 (40.00%) | 6 / 20 (30.00%) | 19 / 37 (51.35%) |
| occurrences (all)                      | 20               | 9               | 37               |
| Swelling of hands                      |                  |                 |                  |
| subjects affected / exposed            | 0 / 25 (0.00%)   | 1 / 20 (5.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)                      | 0                | 1               | 0                |
| Hepatobiliary disorders                |                  |                 |                  |
| Hepatic haemorrhage                    |                  |                 |                  |
| subjects affected / exposed            | 0 / 25 (0.00%)   | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)                      | 0                | 0               | 1                |
| Hyperbilirubinaemia                    |                  |                 |                  |
| subjects affected / exposed            | 0 / 25 (0.00%)   | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)                      | 0                | 0               | 1                |
| Hypertransaminasaemia                  |                  |                 |                  |
| subjects affected / exposed            | 0 / 25 (0.00%)   | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)                      | 0                | 0               | 2                |
| Liver pain                             |                  |                 |                  |
| subjects affected / exposed            | 0 / 25 (0.00%)   | 2 / 20 (10.00%) | 1 / 37 (2.70%)   |
| occurrences (all)                      | 0                | 2               | 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 | 7 / 25 (28.00%) | 7 / 20 (35.00%) | 11 / 37 (29.73%) |
| occurrences (all)           | 8               | 12              | 21               |
| Rash acneiform              |                 |                 |                  |
| subjects affected / exposed | 9 / 25 (36.00%) | 8 / 20 (40.00%) | 13 / 37 (35.14%) |
| occurrences (all)           | 12              | 12              | 19               |
| Rash face                   |                 |                 |                  |
| subjects affected / exposed | 2 / 25 (8.00%)  | 2 / 20 (10.00%) | 1 / 37 (2.70%)   |
| occurrences (all)           | 2               | 2               | 1                |
| Rosacea                     |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)           | 0               | 1               | 0                |
| Seborrhoeic dermatitis      |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)           | 0               | 1               | 0                |
| Skin lesion                 |                 |                 |                  |
| subjects affected / exposed | 1 / 25 (4.00%)  | 0 / 20 (0.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)           | 1               | 0               | 0                |
| Skin oedema                 |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 1 / 20 (5.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)           | 0               | 1               | 0                |
| Skin peeling                |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)           | 0               | 0               | 1                |
| Skin rash                   |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 3 / 20 (15.00%) | 0 / 37 (0.00%)   |
| occurrences (all)           | 0               | 5               | 0                |
| Skin toxicity               |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 0 / 20 (0.00%)  | 2 / 37 (5.41%)   |
| occurrences (all)           | 0               | 0               | 4                |
| Rash on Legs and Arms       |                 |                 |                  |
| subjects affected / exposed | 0 / 25 (0.00%)  | 0 / 20 (0.00%)  | 1 / 37 (2.70%)   |
| occurrences (all)           | 0               | 0               | 1                |
| Renal and urinary disorders |                 |                 |                  |
| Haematuria                  |                 |                 |                  |
| subjects affected / exposed | 1 / 25 (4.00%)  | 0 / 20 (0.00%)  | 0 / 37 (0.00%)   |
| occurrences (all)           | 1               | 0               | 0                |

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

|                              |                |                 |                |
|------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed  | 0 / 25 (0.00%) | 3 / 20 (15.00%) | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 3               | 1              |
| Myalgia of lower extremities |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0               | 1              |
| Neck pain                    |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0               | 1              |
| Osteoarticular pain          |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 1               | 0              |
| Osteonecrosis of jaw         |                |                 |                |
| subjects affected / exposed  | 1 / 25 (4.00%) | 0 / 20 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 1              | 0               | 0              |
| Pain in hip                  |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 3               | 0              |
| Pain in jaw                  |                |                 |                |
| subjects affected / exposed  | 1 / 25 (4.00%) | 0 / 20 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 3              | 0               | 0              |
| Painful hips                 |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0               | 1              |
| Shoulder pain                |                |                 |                |
| subjects affected / exposed  | 2 / 25 (8.00%) | 0 / 20 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 2              | 0               | 0              |
| Infections and infestations  |                |                 |                |
| Abdominal abscess            |                |                 |                |
| subjects affected / exposed  | 1 / 25 (4.00%) | 0 / 20 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 1              | 0               | 0              |
| Candida infection            |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 0 / 20 (0.00%)  | 1 / 37 (2.70%) |
| occurrences (all)            | 0              | 0               | 1              |
| Device related infection     |                |                 |                |
| subjects affected / exposed  | 0 / 25 (0.00%) | 1 / 20 (5.00%)  | 0 / 37 (0.00%) |
| occurrences (all)            | 0              | 1               | 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<br>subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>2   | 1 / 20 (5.00%)<br>1  | 1 / 37 (2.70%)<br>1 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 1 / 25 (4.00%)<br>1   | 0 / 20 (0.00%)<br>0  | 2 / 37 (5.41%)<br>3 |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 25 (4.00%)<br>1   | 0 / 20 (0.00%)<br>0  | 0 / 37 (0.00%)<br>0 |
| Metabolism and nutrition disorders  |                       |                      |                     |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 25 (0.00%)<br>0   | 0 / 20 (0.00%)<br>0  | 1 / 37 (2.70%)<br>1 |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 0 / 25 (0.00%)<br>0   | 0 / 20 (0.00%)<br>0  | 1 / 37 (2.70%)<br>1 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 25 (0.00%)<br>0   | 0 / 20 (0.00%)<br>0  | 1 / 37 (2.70%)<br>1 |
| Gout<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 25 (0.00%)<br>0   | 1 / 20 (5.00%)<br>1  | 1 / 37 (2.70%)<br>1 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 25 (0.00%)<br>0   | 1 / 20 (5.00%)<br>1  | 1 / 37 (2.70%)<br>1 |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                  | 7 / 25 (28.00%)<br>10 | 3 / 20 (15.00%)<br>4 | 3 / 37 (8.11%)<br>5 |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 25 (4.00%)<br>2   | 0 / 20 (0.00%)<br>0  | 0 / 37 (0.00%)<br>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<br>Belfast site Principal Investigator (PI) - notice of change of status.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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.

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.

Notes: