



## Clinical trial results:

**A phase II, open-label, single-arm, non-randomized, multi-center study to evaluate the efficacy of oral TKI258 as second-line therapy in patients with**

**either FGFR2 mutated or wild-type advanced and/or metastatic endometrial cancer**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-000266-35 |
| Trial protocol           | IT ES GB       |
| Global end of trial date | 26 March 2014  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 July 2016 |
| First version publication date | 30 July 2015 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CTKI258A2211 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01379534 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                   |
|------------------------------|-------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                                |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                      |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111<br>, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111<br>, |

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                       | 26 March 2014 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 March 2014 |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

To assess the antitumor activity of TKI258, as measured by an 18-week progression free survival (PFS) rate, in patients with pre-treated endometrial cancer, with or without FGFR2 mutation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

In addition to receiving the study treatment, all patients were to receive best supportive care (BSC, define as; drug or non-drug therapies, nutritional support, physical therapy, or any other treatment alternative that the Investigator believes to be in the patient's best interest, but excluding other antineoplastic treatments) as per standard local practice for the treatment of pre-existing medical conditions or AEs that could arise during the study.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 28 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 6          |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Italy: 8          |
| Country: Number of subjects enrolled | United States: 33 |
| Country: Number of subjects enrolled | New Zealand: 3    |
| Country: Number of subjects enrolled | Brazil: 1         |
| Worldwide total number of subjects   | 53                |
| EEA total number of subjects         | 16                |

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|                                           |    |
|-------------------------------------------|----|
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 24 |
| From 65 to 84 years                       | 29 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were treated with TKI258 until disease progression, unacceptable toxicity, death or discontinuation due to any other reason. All participants were followed for at least 30 days after their last dose of study drug for safety assessment. The treatment and followup periods were combined for patient disposition (listing 16.2.1-1.1).

### Pre-assignment

Screening details:

Either archival tumor tissue or a fresh fixed biopsy was required for the FGFR2 mutation analysis. Only the FGFR2 mutation analysis results during a molecular pre-screening period were used to classify patients into Group 1 (FGFR2 mutated - MUT) or Group 2 (FGFR2 wild type - WT) and if could not be determined, patient was a screen failure.

### Period 1

|                              |                                                  |
|------------------------------|--------------------------------------------------|
| Period 1 title               | Treatment/Tumor Followup Phases (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>             | FGFR2 (MUT) |

Arm description:

Participants were diagnosed with mutational status of FGFR2 as mutated and treated with 500 mg of TKI258 on a 5 day on / 2 days off dosing regimen for 13 weeks.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Mutational status of FGFR2 |
| Investigational medicinal product name | Dovitinib                  |
| Investigational medicinal product code | TKI258                     |
| Other name                             |                            |
| Pharmaceutical forms                   | Tablet                     |
| Routes of administration               | Oral use                   |

Dosage and administration details:

Dovitinib was dosed on a flat scale of 500 mg (i.e., five 100 mg tablets), administered orally on a 5 days on / 2 days off schedule which was repeated every week (i.e., every 7 days). Patients were instructed to swallow the required number of tablets at approximately the same time each day, except on the days of PK sampling.

- Dovitinib could be ingested with or without food, including days on which blood samples were drawn for PK analyses.
- On the days of PK sampling, patients were instructed to bring their dose of dovitinib to the Investigative site whereby the administration of dovitinib was supervised by the site's study personnel. For patients who were unable to tolerate the protocol-specified dosing scheme, dose reductions or delays were permitted to manage dovitinib-related toxicities.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | FGFR2 (WT) |
|------------------|------------|

Arm description:

Participants were diagnosed with mutational status of FGFR2 as wild type and treated with 500 mg of TKI258 on a 5 day on / 2 days off dosing regimen for 13 weeks.

|                                        |            |
|----------------------------------------|------------|
| Arm type                               | tumor type |
| Investigational medicinal product name | Dovitinib  |
| Investigational medicinal product code | TKI258     |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

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**Dosage and administration details:**

Dovitinib was dosed on a flat scale of 500 mg (i.e., five 100 mg tablets), administered orally on a 5 days on / 2 days off schedule which was repeated every week (i.e., every 7 days). Patients were instructed to swallow the required number of tablets at approximately the same time each day, except on the days of PK sampling.

- Dovitinib could be ingested with or without food, including days on which blood samples were drawn for PK analyses.
- On the days of PK sampling, patients were instructed to bring their dose of dovitinib to the Investigative site whereby the administration of dovitinib was supervised by the site's study personnel. For patients who were unable to tolerate the protocol-specified dosing scheme, dose reductions or delays were permitted to manage dovitinib-related toxicities.

| <b>Number of subjects in period 1</b> | <b>FGFR2 (MUT)</b> | <b>FGFR2 (WT)</b> |
|---------------------------------------|--------------------|-------------------|
| Started                               | 22                 | 31                |
| Completed                             | 0                  | 0                 |
| Not completed                         | 22                 | 31                |
| Adverse event, serious fatal          | -                  | 1                 |
| Consent withdrawn by subject          | 2                  | 2                 |
| Adverse event, non-fatal              | 4                  | 5                 |
| Lost to follow-up                     | -                  | 1                 |
| Lack of efficacy                      | 16                 | 22                |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | FGFR2 (MUT) |
|-----------------------|-------------|

Reporting group description:

Participants were diagnosed with mutational status of FGFR2 as mutated and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.

|                       |            |
|-----------------------|------------|
| Reporting group title | FGFR2 (WT) |
|-----------------------|------------|

Reporting group description:

Participants were diagnosed with mutational status of FGFR2 as wild type and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.

| Reporting group values | FGFR2 (MUT) | FGFR2 (WT) | Total |
|------------------------|-------------|------------|-------|
| Number of subjects     | 22          | 31         | 53    |
| Age categorical        |             |            |       |
| Units: Subjects        |             |            |       |
| Adults (18-64 years)   | 11          | 13         | 24    |
| From 65-84 years       | 11          | 18         | 29    |
| Gender categorical     |             |            |       |
| Units: Subjects        |             |            |       |
| Female                 | 22          | 31         | 53    |

## End points

### End points reporting groups

|                                                                                                                                                                   |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                                                                             | FGFR2 (MUT) |
| Reporting group description:                                                                                                                                      |             |
| Participants were diagnosed with mutational status of FGFR2 as mutated and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.   |             |
| Reporting group title                                                                                                                                             | FGFR2 (WT)  |
| Reporting group description:                                                                                                                                      |             |
| Participants were diagnosed with mutational status of FGFR2 as wild type and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks. |             |

### Primary: Progression Free Survival (PFS) Rate

|                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                            | Progression Free Survival (PFS) Rate <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                     |                                                     |
| The 18-week PFS was defined as the percentage of participants who did not have a progression event at week 18. Participants who progressed, died, had response assessment of unknown (UNK) or discontinued before 18 weeks of observation without progression were counted as "failure". Progressive disease was assessed as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. |                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                             | Primary                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                       |                                                     |
| Up to 18 weeks                                                                                                                                                                                                                                                                                                                                                                                                             |                                                     |

Notes:

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

Justification: The study met the futility boundary for both study groups. The 18-week PFS rate was calculated from the investigator's assessment according to RECIST v1.1 and its posterior distribution using the PAS. Treatment effect was to be concluded if the observed 18-week PFS rate was  $\geq 50\%$  and there was  $\geq 0.95$  probability that the 18-week PFS rate was  $> 20\%$ , i.e. the chance that the 18-week PFS rate was  $\leq 20\%$  was less than 0.05.

Kaplan-Meier method was used with its 95% confidence interval.

| End point values                                  | FGFR2 (MUT)         | FGFR2 (WT)      |  |  |
|---------------------------------------------------|---------------------|-----------------|--|--|
| Subject group type                                | Reporting group     | Reporting group |  |  |
| Number of subjects analysed                       | 22                  | 31              |  |  |
| Units: Percentage of Participants                 |                     |                 |  |  |
| number (confidence interval 95%)                  |                     |                 |  |  |
| Percentage of Participants(Progression Free Rate) | 31.8 (13.9 to 54.9) | 29 (14.2 to 48) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response Rate (ORR)

|                                                                                                         |                             |
|---------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                         | Overall Response Rate (ORR) |
| End point description:                                                                                  |                             |
| ORR is defined as the percentage of participants with a best overall response of complete response (CR) |                             |

or partial response (PR).

|                                                                      |           |
|----------------------------------------------------------------------|-----------|
| End point type                                                       | Secondary |
| End point timeframe:                                                 |           |
| Baseline and every 6 weeks until disease progression, up to 18 weeks |           |

| End point values                  | FGFR2 (MUT)       | FGFR2 (WT)         |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 22                | 31                 |  |  |
| Units: Percentage of Participants |                   |                    |  |  |
| number (confidence interval 95%)  | 4.5 (0.1 to 22.8) | 16.1 (5.5 to 33.7) |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Disease Control Rate (DCR)

|                                                                                                                    |                            |
|--------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                    | Disease Control Rate (DCR) |
| End point description:                                                                                             |                            |
| DCR was defined as the percentage of participants with a best overall response of CR or PR or stable disease (SD). |                            |
| End point type                                                                                                     | Secondary                  |
| End point timeframe:                                                                                               |                            |
| Baseline and every 6 weeks until disease progression, up to 18 weeks                                               |                            |

| End point values                  | FGFR2 (MUT)         | FGFR2 (WT)          |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 22                  | 31                  |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 63.6 (40.7 to 82.8) | 51.6 (33.1 to 69.8) |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Duration of Response (DR)

|                                                                                                             |                           |
|-------------------------------------------------------------------------------------------------------------|---------------------------|
| End point title                                                                                             | Duration of Response (DR) |
| End point description:                                                                                      |                           |
| This outcome measure was not analyzed. The analysis was not required because there were too few responders. |                           |



|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| up to 18 weeks       |           |

| End point values                          | FGFR2 (MUT)      | FGFR2 (WT)       |  |  |
|-------------------------------------------|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 0 <sup>[2]</sup> | 0 <sup>[3]</sup> |  |  |
| Units: Time to Event                      |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | ( to )           | ( to )           |  |  |

Notes:

[2] - The analysis was not required because there were too few responders.

[3] - The analysis was not required because there were too few responders.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                     |                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                     | Overall Survival (OS) |
| End point description:                                                                                                                                                                                                                                                                                                              |                       |
| OS was defined as the time from date of treatment to the date of death from any cause. If a participant was not known to have died at the date of analysis cut-off, the OS was censored at the last date of contact. Full Analysis Set (FAS): The FAS included all participants who received at least one dose of study medication. |                       |
| End point type                                                                                                                                                                                                                                                                                                                      | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                |                       |
| Up to 18 weeks                                                                                                                                                                                                                                                                                                                      |                       |

| End point values                 | FGFR2 (MUT)        | FGFR2 (WT)      |  |  |
|----------------------------------|--------------------|-----------------|--|--|
| Subject group type               | Reporting group    | Reporting group |  |  |
| Number of subjects analysed      | 22                 | 31              |  |  |
| Units: Months                    |                    |                 |  |  |
| median (confidence interval 95%) | 20.2 (8.2 to 20.2) | 9.3 (6 to 15.2) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS)

|                                                                                                                                                                                                            |                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                            | Progression Free Survival (PFS) |
| End point description:                                                                                                                                                                                     |                                 |
| PFS was defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. If a participant did not have an event, PFS was censored at the |                                 |

date of last adequate response assessment before the data analysis cut-off date or the start date of new antineoplastic therapy after study drug discontinuation.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 18 weeks       |           |

| End point values                 | FGFR2 (MUT)      | FGFR2 (WT)       |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 22               | 31               |  |  |
| Units: Months                    |                  |                  |  |  |
| median (confidence interval 95%) | 4.1 (2.6 to 5.5) | 2.7 (1.4 to 6.8) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Adverse Events, Serious Adverse Events and Deaths

|                                                                 |                                                                               |
|-----------------------------------------------------------------|-------------------------------------------------------------------------------|
| End point title                                                 | Number of Participants With Adverse Events, Serious Adverse Events and Deaths |
| End point description:                                          |                                                                               |
| Adverse event monitoring was conducted throughout the study.    |                                                                               |
| End point type                                                  | Secondary                                                                     |
| End point timeframe:                                            |                                                                               |
| up to 30 days after the last dose of study drug, up to 18 weeks |                                                                               |

| End point values                         | FGFR2 (MUT)     | FGFR2 (WT)      |  |  |
|------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 22              | 31              |  |  |
| Units: Participants                      |                 |                 |  |  |
| Adverse Events (serious and non-serious) | 22              | 31              |  |  |
| Serious adverse events                   | 10              | 20              |  |  |
| Deaths                                   | 1               | 4               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.0   |

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | FGFR2 WT |
|-----------------------|----------|

Reporting group description:

Participants diagnosed with FGFR2 as wild type were dosed with TKI258 on a flat scale of 500mg administered orally on a 5 days on /2 days off schedule which was repeated every week (i.e., every 7 days)

|                       |           |
|-----------------------|-----------|
| Reporting group title | FGFR2 MUT |
|-----------------------|-----------|

Reporting group description:

Participants with FGFR2 as mutated were treated with 500 mg of TKI258 orally on a 5 day on/2 days off dosing regimen which was repeated every week (i.e., every 7 days)

| Serious adverse events                            | FGFR2 WT         | FGFR2 MUT        |  |
|---------------------------------------------------|------------------|------------------|--|
| Total subjects affected by serious adverse events |                  |                  |  |
| subjects affected / exposed                       | 20 / 31 (64.52%) | 10 / 22 (45.45%) |  |
| number of deaths (all causes)                     | 4                | 1                |  |
| number of deaths resulting from adverse events    | 1                | 0                |  |
| Vascular disorders                                |                  |                  |  |
| DEEP VEIN THROMBOSIS                              |                  |                  |  |
| subjects affected / exposed                       | 0 / 31 (0.00%)   | 2 / 22 (9.09%)   |  |
| occurrences causally related to treatment / all   | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| EMBOLISM                                          |                  |                  |  |
| subjects affected / exposed                       | 2 / 31 (6.45%)   | 1 / 22 (4.55%)   |  |
| occurrences causally related to treatment / all   | 1 / 2            | 1 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| HYPOTENSION                                       |                  |                  |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 2 / 31 (6.45%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| HYPERTENSION                                         |                |                |  |
| subjects affected / exposed                          | 2 / 31 (6.45%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all      | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| ORTHOSTATIC HYPOTENSION                              |                |                |  |
| subjects affected / exposed                          | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| PELVIC VENOUS THROMBOSIS                             |                |                |  |
| subjects affected / exposed                          | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| PERIPHERAL ISCHAEMIA                                 |                |                |  |
| subjects affected / exposed                          | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| FATIGUE                                              |                |                |  |
| subjects affected / exposed                          | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| LOCALISED OEDEMA                                     |                |                |  |
| subjects affected / exposed                          | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| PYREXIA                                              |                |                |  |
| subjects affected / exposed                          | 2 / 31 (6.45%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| OEDEMA PERIPHERAL                                    |                |                |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 31 (6.45%) | 0 / 22 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| MALAISE                                         |                |                 |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Reproductive system and breast disorders        |                |                 |  |
| FEMALE GENITAL TRACT FISTULA                    |                |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%) | 0 / 22 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| VAGINAL HAEMORRHAGE                             |                |                 |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 1 / 22 (4.55%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| PLEURAL EFFUSION                                |                |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%) | 0 / 22 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| LUNG INFILTRATION                               |                |                 |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| PNEUMONIA ASPIRATION                            |                |                 |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| PULMONARY EMBOLISM                              |                |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%) | 3 / 22 (13.64%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 2 / 3           |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0           |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| RESPIRATORY FAILURE                             |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| ASPARTATE AMINOTRANSFERASE INCREASED            |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ALANINE AMINOTRANSFERASE INCREASED              |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| TRANSAMINASES INCREASED                         |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| BLOOD BILIRUBIN INCREASED                       |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PLATELET COUNT DECREASED                        |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| GASTROENTERITIS RADIATION                       |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Congenital, familial and genetic disorders      |                |                |  |
| GASTROINTESTINAL ARTERIOVENOUS MALFORMATION     |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| CARDIAC ARREST                                  |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| CEREBROVASCULAR ACCIDENT                        |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HEADACHE                                        |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PERIPHERAL SENSORY NEUROPATHY                   |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SPINAL CORD COMPRESSION                         |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SYNCOPE                                         |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| TRANSIENT ISCHAEMIC ATTACK                      |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| ANAEMIA                                         |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PANCYTOPENIA                                    |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| ABDOMINAL PAIN                                  |                |                |  |
| subjects affected / exposed                     | 2 / 31 (6.45%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| ABDOMINAL PAIN UPPER                            |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| COLITIS ISCHAEMIC                               |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DIARRHOEA                                       |                |                |  |
| subjects affected / exposed                     | 3 / 31 (9.68%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 2 / 3          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| LOWER GASTROINTESTINAL HAEMORRHAGE              |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DYSPHAGIA                                       |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |



|                                                 |                 |                |  |
|-------------------------------------------------|-----------------|----------------|--|
| NAUSEA                                          |                 |                |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| PANCREATIC DUCT DILATATION                      |                 |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%)  | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| SMALL INTESTINAL OBSTRUCTION                    |                 |                |  |
| subjects affected / exposed                     | 3 / 31 (9.68%)  | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| VOMITING                                        |                 |                |  |
| subjects affected / exposed                     | 5 / 31 (16.13%) | 2 / 22 (9.09%) |  |
| occurrences causally related to treatment / all | 2 / 6           | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatobiliary disorders                         |                 |                |  |
| HEPATITIS TOXIC                                 |                 |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%)  | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| JAUNDICE                                        |                 |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%)  | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                 |                |  |
| ERYTHEMA MULTIFORME                             |                 |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%)  | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal and urinary disorders                     |                 |                |  |
| HYDRONEPHROSIS                                  |                 |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RENAL FAILURE                                   |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| URINARY TRACT OBSTRUCTION                       |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RENAL FAILURE ACUTE                             |                |                |  |
| subjects affected / exposed                     | 2 / 31 (6.45%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| UROGENITAL FISTULA                              |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| GROIN PAIN                                      |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PAIN IN EXTREMITY                               |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| SEPSIS                                          |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| URINARY TRACT INFECTION                         |                |                |  |
| subjects affected / exposed                     | 2 / 31 (6.45%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| UROSEPSIS                                       |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Metabolism and nutrition disorders              |                |                |  |
| DECREASED APPETITE                              |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DEHYDRATION                                     |                |                |  |
| subjects affected / exposed                     | 3 / 31 (9.68%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 2 / 3          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HYPOVOLAEMIA                                    |                |                |  |
| subjects affected / exposed                     | 0 / 31 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HYPONATRAEMIA                                   |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HYPOKALAEMIA                                    |                |                |  |
| subjects affected / exposed                     | 1 / 31 (3.23%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | FGFR2 WT          | FGFR2 MUT        |  |
|-------------------------------------------------------|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                   |                  |  |
| subjects affected / exposed                           | 31 / 31 (100.00%) | 21 / 22 (95.45%) |  |
| Vascular disorders                                    |                   |                  |  |
| DEEP VEIN THROMBOSIS                                  |                   |                  |  |
| subjects affected / exposed                           | 2 / 31 (6.45%)    | 1 / 22 (4.55%)   |  |
| occurrences (all)                                     | 2                 | 1                |  |
| EMBOLISM                                              |                   |                  |  |
| subjects affected / exposed                           | 1 / 31 (3.23%)    | 2 / 22 (9.09%)   |  |
| occurrences (all)                                     | 1                 | 2                |  |
| HYPERTENSION                                          |                   |                  |  |
| subjects affected / exposed                           | 8 / 31 (25.81%)   | 4 / 22 (18.18%)  |  |
| occurrences (all)                                     | 17                | 8                |  |
| HYPOTENSION                                           |                   |                  |  |
| subjects affected / exposed                           | 2 / 31 (6.45%)    | 2 / 22 (9.09%)   |  |
| occurrences (all)                                     | 3                 | 2                |  |
| General disorders and administration site conditions  |                   |                  |  |
| FATIGUE                                               |                   |                  |  |
| subjects affected / exposed                           | 16 / 31 (51.61%)  | 9 / 22 (40.91%)  |  |
| occurrences (all)                                     | 19                | 10               |  |
| ASTHENIA                                              |                   |                  |  |
| subjects affected / exposed                           | 5 / 31 (16.13%)   | 4 / 22 (18.18%)  |  |
| occurrences (all)                                     | 5                 | 5                |  |
| LOCAL SWELLING                                        |                   |                  |  |
| subjects affected / exposed                           | 0 / 31 (0.00%)    | 2 / 22 (9.09%)   |  |
| occurrences (all)                                     | 0                 | 2                |  |
| OEDEMA PERIPHERAL                                     |                   |                  |  |
| subjects affected / exposed                           | 4 / 31 (12.90%)   | 2 / 22 (9.09%)   |  |
| occurrences (all)                                     | 6                 | 3                |  |
| PAIN                                                  |                   |                  |  |
| subjects affected / exposed                           | 6 / 31 (19.35%)   | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 7                 | 0                |  |
| Reproductive system and breast disorders              |                   |                  |  |
| VAGINAL HAEMORRHAGE                                   |                   |                  |  |
| subjects affected / exposed                           | 1 / 31 (3.23%)    | 3 / 22 (13.64%)  |  |
| occurrences (all)                                     | 1                 | 3                |  |

|                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                   |                                                                                                                                 |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--|
| VAGINAL DISCHARGE<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                         | 2 / 31 (6.45%)<br>2                                                                                                               | 1 / 22 (4.55%)<br>1                                                                                                             |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)<br><br>EPISTAXIS<br>subjects affected / exposed<br>occurrences (all)<br><br>DYSпноEA<br>subjects affected / exposed<br>occurrences (all)<br><br>PLEURITIC PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>OROPHARYNGEAL PAIN<br>subjects affected / exposed<br>occurrences (all) | 6 / 31 (19.35%)<br>6<br><br>3 / 31 (9.68%)<br>3<br><br>7 / 31 (22.58%)<br>8<br><br>2 / 31 (6.45%)<br>2<br><br>2 / 31 (6.45%)<br>2 | 2 / 22 (9.09%)<br>3<br><br>0 / 22 (0.00%)<br>0<br><br>2 / 22 (9.09%)<br>2<br><br>0 / 22 (0.00%)<br>0<br><br>0 / 22 (0.00%)<br>0 |  |
| Psychiatric disorders<br>ANXIETY<br>subjects affected / exposed<br>occurrences (all)<br><br>INSOMNIA<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                      | 2 / 31 (6.45%)<br>2<br><br>2 / 31 (6.45%)<br>2                                                                                    | 0 / 22 (0.00%)<br>0<br><br>2 / 22 (9.09%)<br>2                                                                                  |  |
| Investigations<br>AMYLASE INCREASED<br>subjects affected / exposed<br>occurrences (all)<br><br>ALANINE AMINOTRANSFERASE INCREASED<br>subjects affected / exposed<br>occurrences (all)<br><br>ASPARTATE AMINOTRANSFERASE INCREASED                                                                                                                                                                             | 2 / 31 (6.45%)<br>2<br><br>3 / 31 (9.68%)<br>4                                                                                    | 0 / 22 (0.00%)<br>0<br><br>4 / 22 (18.18%)<br>5                                                                                 |  |

|                                                |                 |                 |  |
|------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                    | 2 / 31 (6.45%)  | 3 / 22 (13.64%) |  |
| occurrences (all)                              | 3               | 4               |  |
| BLOOD ALKALINE PHOSPHATASE INCREASED           |                 |                 |  |
| subjects affected / exposed                    | 8 / 31 (25.81%) | 3 / 22 (13.64%) |  |
| occurrences (all)                              | 10              | 4               |  |
| BLOOD BILIRUBIN INCREASED                      |                 |                 |  |
| subjects affected / exposed                    | 0 / 31 (0.00%)  | 2 / 22 (9.09%)  |  |
| occurrences (all)                              | 0               | 2               |  |
| BLOOD CHOLESTEROL INCREASED                    |                 |                 |  |
| subjects affected / exposed                    | 3 / 31 (9.68%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                              | 3               | 1               |  |
| BLOOD CREATININE INCREASED                     |                 |                 |  |
| subjects affected / exposed                    | 4 / 31 (12.90%) | 3 / 22 (13.64%) |  |
| occurrences (all)                              | 5               | 3               |  |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED            |                 |                 |  |
| subjects affected / exposed                    | 2 / 31 (6.45%)  | 2 / 22 (9.09%)  |  |
| occurrences (all)                              | 2               | 2               |  |
| LIPASE INCREASED                               |                 |                 |  |
| subjects affected / exposed                    | 2 / 31 (6.45%)  | 2 / 22 (9.09%)  |  |
| occurrences (all)                              | 2               | 5               |  |
| LYMPHOCYTE COUNT DECREASED                     |                 |                 |  |
| subjects affected / exposed                    | 2 / 31 (6.45%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                              | 3               | 3               |  |
| PLATELET COUNT DECREASED                       |                 |                 |  |
| subjects affected / exposed                    | 2 / 31 (6.45%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                              | 2               | 1               |  |
| WEIGHT DECREASED                               |                 |                 |  |
| subjects affected / exposed                    | 5 / 31 (16.13%) | 7 / 22 (31.82%) |  |
| occurrences (all)                              | 7               | 8               |  |
| Injury, poisoning and procedural complications |                 |                 |  |
| CONTUSION                                      |                 |                 |  |
| subjects affected / exposed                    | 2 / 31 (6.45%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                              | 2               | 0               |  |
| FALL                                           |                 |                 |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 31 (6.45%)<br>2 | 0 / 22 (0.00%)<br>0 |  |
| Nervous system disorders                         |                     |                     |  |
| DIZZINESS                                        |                     |                     |  |
| subjects affected / exposed                      | 7 / 31 (22.58%)     | 3 / 22 (13.64%)     |  |
| occurrences (all)                                | 9                   | 4                   |  |
| PARAESTHESIA                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 31 (0.00%)      | 2 / 22 (9.09%)      |  |
| occurrences (all)                                | 0                   | 3                   |  |
| HEADACHE                                         |                     |                     |  |
| subjects affected / exposed                      | 6 / 31 (19.35%)     | 5 / 22 (22.73%)     |  |
| occurrences (all)                                | 7                   | 5                   |  |
| DYSGEUSIA                                        |                     |                     |  |
| subjects affected / exposed                      | 2 / 31 (6.45%)      | 2 / 22 (9.09%)      |  |
| occurrences (all)                                | 2                   | 2                   |  |
| SOMNOLENCE                                       |                     |                     |  |
| subjects affected / exposed                      | 2 / 31 (6.45%)      | 0 / 22 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| Blood and lymphatic system disorders             |                     |                     |  |
| LYMPHOPENIA                                      |                     |                     |  |
| subjects affected / exposed                      | 3 / 31 (9.68%)      | 1 / 22 (4.55%)      |  |
| occurrences (all)                                | 4                   | 1                   |  |
| ANAEMIA                                          |                     |                     |  |
| subjects affected / exposed                      | 10 / 31 (32.26%)    | 3 / 22 (13.64%)     |  |
| occurrences (all)                                | 16                  | 5                   |  |
| LEUKOPENIA                                       |                     |                     |  |
| subjects affected / exposed                      | 2 / 31 (6.45%)      | 0 / 22 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| NEUTROPENIA                                      |                     |                     |  |
| subjects affected / exposed                      | 2 / 31 (6.45%)      | 1 / 22 (4.55%)      |  |
| occurrences (all)                                | 2                   | 3                   |  |
| THROMBOCYTOPENIA                                 |                     |                     |  |
| subjects affected / exposed                      | 4 / 31 (12.90%)     | 0 / 22 (0.00%)      |  |
| occurrences (all)                                | 5                   | 0                   |  |
| Ear and labyrinth disorders                      |                     |                     |  |

|                                                                          |                        |                        |  |
|--------------------------------------------------------------------------|------------------------|------------------------|--|
| TINNITUS<br>subjects affected / exposed<br>occurrences (all)             | 2 / 31 (6.45%)<br>2    | 0 / 22 (0.00%)<br>0    |  |
| Eye disorders                                                            |                        |                        |  |
| EYE DISCHARGE<br>subjects affected / exposed<br>occurrences (all)        | 2 / 31 (6.45%)<br>2    | 0 / 22 (0.00%)<br>0    |  |
| DRY EYE<br>subjects affected / exposed<br>occurrences (all)              | 4 / 31 (12.90%)<br>4   | 2 / 22 (9.09%)<br>2    |  |
| OCULAR HYPERAEMIA<br>subjects affected / exposed<br>occurrences (all)    | 3 / 31 (9.68%)<br>3    | 0 / 22 (0.00%)<br>0    |  |
| VISION BLURRED<br>subjects affected / exposed<br>occurrences (all)       | 2 / 31 (6.45%)<br>2    | 0 / 22 (0.00%)<br>0    |  |
| Gastrointestinal disorders                                               |                        |                        |  |
| ABDOMINAL PAIN<br>subjects affected / exposed<br>occurrences (all)       | 6 / 31 (19.35%)<br>7   | 5 / 22 (22.73%)<br>5   |  |
| ABDOMINAL PAIN LOWER<br>subjects affected / exposed<br>occurrences (all) | 2 / 31 (6.45%)<br>2    | 1 / 22 (4.55%)<br>1    |  |
| ABDOMINAL PAIN UPPER<br>subjects affected / exposed<br>occurrences (all) | 2 / 31 (6.45%)<br>3    | 0 / 22 (0.00%)<br>0    |  |
| CONSTIPATION<br>subjects affected / exposed<br>occurrences (all)         | 6 / 31 (19.35%)<br>9   | 4 / 22 (18.18%)<br>5   |  |
| DRY MOUTH<br>subjects affected / exposed<br>occurrences (all)            | 3 / 31 (9.68%)<br>3    | 3 / 22 (13.64%)<br>4   |  |
| DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)            | 24 / 31 (77.42%)<br>48 | 14 / 22 (63.64%)<br>24 |  |
| DYSPEPSIA                                                                |                        |                        |  |



|                                             |                  |                  |  |
|---------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                 | 5 / 31 (16.13%)  | 4 / 22 (18.18%)  |  |
| occurrences (all)                           | 7                | 4                |  |
| GASTROOESOPHAGEAL REFLUX DISEASE            |                  |                  |  |
| subjects affected / exposed                 | 2 / 31 (6.45%)   | 1 / 22 (4.55%)   |  |
| occurrences (all)                           | 2                | 1                |  |
| FLATULENCE                                  |                  |                  |  |
| subjects affected / exposed                 | 4 / 31 (12.90%)  | 2 / 22 (9.09%)   |  |
| occurrences (all)                           | 4                | 2                |  |
| NAUSEA                                      |                  |                  |  |
| subjects affected / exposed                 | 21 / 31 (67.74%) | 16 / 22 (72.73%) |  |
| occurrences (all)                           | 28               | 19               |  |
| VOMITING                                    |                  |                  |  |
| subjects affected / exposed                 | 21 / 31 (67.74%) | 14 / 22 (63.64%) |  |
| occurrences (all)                           | 32               | 31               |  |
| STOMATITIS                                  |                  |                  |  |
| subjects affected / exposed                 | 2 / 31 (6.45%)   | 1 / 22 (4.55%)   |  |
| occurrences (all)                           | 2                | 1                |  |
| Skin and subcutaneous tissue disorders      |                  |                  |  |
| DERMATITIS ACNEIFORM                        |                  |                  |  |
| subjects affected / exposed                 | 2 / 31 (6.45%)   | 1 / 22 (4.55%)   |  |
| occurrences (all)                           | 2                | 1                |  |
| RASH MACULO-PAPULAR                         |                  |                  |  |
| subjects affected / exposed                 | 0 / 31 (0.00%)   | 2 / 22 (9.09%)   |  |
| occurrences (all)                           | 0                | 3                |  |
| RASH                                        |                  |                  |  |
| subjects affected / exposed                 | 11 / 31 (35.48%) | 9 / 22 (40.91%)  |  |
| occurrences (all)                           | 12               | 9                |  |
| PRURITUS                                    |                  |                  |  |
| subjects affected / exposed                 | 3 / 31 (9.68%)   | 4 / 22 (18.18%)  |  |
| occurrences (all)                           | 3                | 4                |  |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME |                  |                  |  |
| subjects affected / exposed                 | 1 / 31 (3.23%)   | 2 / 22 (9.09%)   |  |
| occurrences (all)                           | 1                | 2                |  |
| Renal and urinary disorders                 |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| DYSURIA                                         |                 |                 |  |
| subjects affected / exposed                     | 4 / 31 (12.90%) | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 4               | 0               |  |
| PROTEINURIA                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 31 (9.68%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 5               | 3               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| ARTHRALGIA                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 2               | 1               |  |
| BACK PAIN                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 6 / 22 (27.27%) |  |
| occurrences (all)                               | 2               | 6               |  |
| BONE PAIN                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 2               | 0               |  |
| MUSCLE SPASMS                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 31 (9.68%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 4               | 3               |  |
| PAIN IN EXTREMITY                               |                 |                 |  |
| subjects affected / exposed                     | 9 / 31 (29.03%) | 6 / 22 (27.27%) |  |
| occurrences (all)                               | 9               | 8               |  |
| MYALGIA                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 2 / 22 (9.09%)  |  |
| occurrences (all)                               | 2               | 3               |  |
| MUSCULOSKELETAL PAIN                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 31 (9.68%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 3               | 0               |  |
| MUSCULAR WEAKNESS                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 2               | 0               |  |
| Infections and infestations                     |                 |                 |  |
| UPPER RESPIRATORY TRACT INFECTION               |                 |                 |  |
| subjects affected / exposed                     | 2 / 31 (6.45%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 4               | 0               |  |
| URINARY TRACT INFECTION                         |                 |                 |  |

|                                                  |                     |                      |  |
|--------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 31 (9.68%)<br>5 | 3 / 22 (13.64%)<br>3 |  |
| Metabolism and nutrition disorders               |                     |                      |  |
| DECREASED APPETITE                               |                     |                      |  |
| subjects affected / exposed                      | 9 / 31 (29.03%)     | 9 / 22 (40.91%)      |  |
| occurrences (all)                                | 10                  | 10                   |  |
| DEHYDRATION                                      |                     |                      |  |
| subjects affected / exposed                      | 5 / 31 (16.13%)     | 1 / 22 (4.55%)       |  |
| occurrences (all)                                | 8                   | 1                    |  |
| HYPERCHOLESTEROLAEMIA                            |                     |                      |  |
| subjects affected / exposed                      | 4 / 31 (12.90%)     | 1 / 22 (4.55%)       |  |
| occurrences (all)                                | 4                   | 1                    |  |
| HYPERGLYCAEMIA                                   |                     |                      |  |
| subjects affected / exposed                      | 5 / 31 (16.13%)     | 2 / 22 (9.09%)       |  |
| occurrences (all)                                | 8                   | 2                    |  |
| HYPOALBUMINAEMIA                                 |                     |                      |  |
| subjects affected / exposed                      | 5 / 31 (16.13%)     | 1 / 22 (4.55%)       |  |
| occurrences (all)                                | 8                   | 1                    |  |
| HYPERTRIGLYCERIDAEMIA                            |                     |                      |  |
| subjects affected / exposed                      | 9 / 31 (29.03%)     | 2 / 22 (9.09%)       |  |
| occurrences (all)                                | 10                  | 8                    |  |
| HYPOCALCAEMIA                                    |                     |                      |  |
| subjects affected / exposed                      | 4 / 31 (12.90%)     | 0 / 22 (0.00%)       |  |
| occurrences (all)                                | 5                   | 0                    |  |
| HYPOMAGNESAEMIA                                  |                     |                      |  |
| subjects affected / exposed                      | 6 / 31 (19.35%)     | 4 / 22 (18.18%)      |  |
| occurrences (all)                                | 7                   | 5                    |  |
| HYPONATRAEMIA                                    |                     |                      |  |
| subjects affected / exposed                      | 5 / 31 (16.13%)     | 1 / 22 (4.55%)       |  |
| occurrences (all)                                | 6                   | 1                    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 October 2011  | The protocol was amended to remove the exploratory analysis of plasma biomarkers FGF23 and FGF19 from this study. The scientific rationale for removing these plasma biomarkers was that sufficient samples were collected in the phase I and phase II studies, and indirect proof of FGFR1 inhibition by dovitinib (increase in plasma FGF23) was obtained in clinical trials. |
| 01 July 2012     | The primary purpose of this protocol amendment was to allow dovitinib to be administered with or without food. New clinical data had shown no clinically relevant food-effect on the exposure of dovitinib.                                                                                                                                                                     |
| 08 November 2013 | The primary purpose of this protocol amendment was to update the clinical PK and concomitant medications sections of the protocol based on preliminary PK findings from CTKI258A2119, a drug-drug interaction study which assessed the effect of dovitinib on the PK of caffeine, diclofenac, omeprazole, and midazolam.                                                        |

Notes:

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### 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.

The study met the protocol defined futility boundary for both the FGFR2 mutated and FGFR2 wild-type groups at the interim analysis as defined by the protocol and did not continue to Stage 2.

Notes: