



## Clinical trial results:

### **An open-label phase IIIb study of regorafenib in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2011-005836-25                                     |
| Trial protocol           | BE DE CZ ES GB IT AT NL IE FR PT FI SE GR HU PL DK |
| Global end of trial date | 02 January 2015                                    |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 02 July 2016 |
| First version publication date | 02 July 2016 |

## Trial information

### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | BAY73-4506 / 15967 |
|-----------------------|--------------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01538680 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bayer HealthCare AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,                                     |
| Public contact               | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com |
| Scientific contact           | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com |

Notes:

## Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 02 January 2015 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 02 January 2015 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The objectives of this study were:

- to provide regorafenib to subjects diagnosed with metastatic colorectal cancer who had failed after all approved standard therapies,
- to assess the safety of regorafenib, and
- to estimate progression-free survival (PFS).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 02 April 2012 |
| 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 | Australia: 87      |
| Country: Number of subjects enrolled | Austria: 46        |
| Country: Number of subjects enrolled | Belgium: 172       |
| Country: Number of subjects enrolled | Czech Republic: 39 |
| Country: Number of subjects enrolled | Denmark: 24        |
| Country: Number of subjects enrolled | Finland: 16        |
| Country: Number of subjects enrolled | France: 329        |
| Country: Number of subjects enrolled | Germany: 327       |
| Country: Number of subjects enrolled | Greece: 28         |
| Country: Number of subjects enrolled | Hungary: 11        |
| Country: Number of subjects enrolled | Ireland: 11        |
| Country: Number of subjects enrolled | Italy: 686         |
| Country: Number of subjects enrolled | Netherlands: 33    |
| Country: Number of subjects enrolled | Norway: 3          |
| Country: Number of subjects enrolled | Poland: 7          |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 14           |
| Country: Number of subjects enrolled | Spain: 308             |
| Country: Number of subjects enrolled | Sweden: 7              |
| Country: Number of subjects enrolled | Switzerland: 39        |
| Country: Number of subjects enrolled | United Kingdom: 27     |
| Country: Number of subjects enrolled | Israel: 113            |
| Country: Number of subjects enrolled | Mexico: 37             |
| Country: Number of subjects enrolled | Russian Federation: 45 |
| Country: Number of subjects enrolled | Canada: 99             |
| Country: Number of subjects enrolled | United States: 364     |
| Worldwide total number of subjects   | 2872                   |
| EEA total number of subjects         | 2088                   |

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)                      | 1720 |
| From 65 to 84 years                       | 1152 |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at centers in Europe, North America (including Mexico), Israel, and Australia. From 02 April 2012 (first subject first visit) to 02 January 2015 (data cut-off date).

### Pre-assignment

Screening details:

Overall, 3309 subjects were screened and enrolled. Of these, a total of 2872 subjects were assigned to receive treatment (trt). A total of 2864 subjects started treatment, and 2851 subjects had terminated treatment at the time of the data cut-off.

### Period 1

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

### Arms

|           |                          |
|-----------|--------------------------|
| Arm title | Regorafenib (BAY73-4506) |
|-----------|--------------------------|

Arm description:

Subjects received regorafenib 160 milligram (mg) (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator's discretion.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Regorafenib  |
| Investigational medicinal product code | BAY73-4506   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects received regorafenib 160 mg (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (i.e. 3 weeks on, 1 week off).

|                                       |                          |
|---------------------------------------|--------------------------|
| <b>Number of subjects in period 1</b> | Regorafenib (BAY73-4506) |
| Started                               | 2872                     |
| Started treatment                     | 2864                     |
| Safety follow-up completed            | 1589 <sup>[1]</sup>      |
| Completed                             | 2851                     |
| Not completed                         | 21                       |
| Study drug never administered         | 8                        |
| On-going                              | 13                       |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: In this study only 1589 subjects completed the safety follow-up 30 days after the last dose of the study. However, this is not a criteria for completing the study. Therefore the number of subjects who completed the study are higher than those who completed the safety follow-up.

## Baseline characteristics

### Reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Regorafenib (BAY73-4506) |
| Reporting group description:   |                          |
| Subjects received regorafenib 160 milligram (mg) (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator's discretion. |                          |

| Reporting group values   | Regorafenib (BAY73-4506) | Total |  |
|--|--------------------------|-------|--|
| Number of subjects   | 2872                     | 2872  |  |
| Age categorical  |                          |       |  |
| Units: Subjects  |                          |       |  |
| Total  |                          |       |  |
| Units: years   |                          |       |  |
| arithmetic mean  | 61.1                     |       |  |
| standard deviation   | ± 10.5                   | -     |  |
| Gender, Male/Female  |                          |       |  |
| Units: subjects  |                          |       |  |
| Female   | 1180                     | 1180  |  |
| Male   | 1692                     | 1692  |  |
| Eastern Cooperative Oncology Group (ECOG) performance status (PS)  |                          |       |  |
| ECOG PS score was measured in a scale of 0-5, where 0= Fully active, able to carry on all pre-disease performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed or chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care. Totally confined to bed or chair and, 5= Death. |                          |       |  |
| Units: Subjects  |                          |       |  |
| 0 = Fully Active   | 1357                     | 1357  |  |
| 1= Restricted Activity   | 1509                     | 1509  |  |
| Missing  | 6                        | 6     |  |
| Histology  |                          |       |  |
| Subjects with relating to disease factors includes Adenocarcinoma, Adenocarcinoma In Situ, Mucinous Carcinoma, Missing were reported.  |                          |       |  |
| Units: Subjects  |                          |       |  |
| Adenocarcinoma   | 2852                     | 2852  |  |
| Adenocarcinoma In Situ   | 15                       | 15    |  |
| Mucinous Carcinoma   | 3                        | 3     |  |
| Missing  | 2                        | 2     |  |
| Primary Site of Disease  |                          |       |  |
| Subjects with primary site of disease (Colon, Rectum, Colon and Rectum) were reported.   |                          |       |  |
| Units: Subjects  |                          |       |  |
| Colon Cancer   | 1846                     | 1846  |  |

|  |             |      |  |
|--|-------------|------|--|
| Rectal Cancer  | 808         | 808  |  |
| Colon and Rectal Cancer  | 217         | 217  |  |
| Missing  | 1           | 1    |  |
| Kirsten rat sarcoma viral oncogene homolog, protein (KRAS) Mutation                                  |             |      |  |
| KRAS Mutation was defined as historical data from the primary tumor, analyzed in local laboratories. |             |      |  |
| Units: Subjects  |             |      |  |
| No   | 1284        | 1284 |  |
| Yes  | 1465        | 1465 |  |
| Unknown  | 122         | 122  |  |
| Missing  | 1           | 1    |  |
| Time Since Initial Diagnosis of Colorectal Cancer to Treatment Assignment                            |             |      |  |
| Treatment assignment was the date of first treatment.  |             |      |  |
| Units: Subjects  |             |      |  |
| Less than (<) 18 months  | 315         | 315  |  |
| Greater than equal ( $\geq$ )18 months   | 2549        | 2549 |  |
| Missing  | 8           | 8    |  |
| Time Since First Diagnosis of Metastatic Disease to Treatment Assignment                             |             |      |  |
| Units: weeks   |             |      |  |
| arithmetic mean  | 158.39      |      |  |
| standard deviation   | $\pm 99.32$ | -    |  |

## End points

### End points reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Regorafenib (BAY73-4506) |
| Reporting group description:   |                          |
| Subjects received regorafenib 160 milligram (mg) (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator's discretion. |                          |

### Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Discontinuation, and Drug Related TEAEs, and Subjects Who Died

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Discontinuation, and Drug Related TEAEs, and Subjects Who Died <sup>[1]</sup> |
|-----------------|---|

#### End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another med important serious event as judged by the invest. Treatment-emergent was defined as any event arising or worsening after the start of study drug admin until 30 days after the last study medication. Safety analysis set (SAF) included all subjects who received at least one dose of study drug. Number of subjects analysed signifies subjects evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

From the start of study treatment up to 30 days after the last dose of study drug, assessed up to 33 months

#### 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                         | Regorafenib (BAY73-4506) |  |  |  |
|--|--------------------------|--|--|--|
| Subject group type                       | Reporting group          |  |  |  |
| Number of subjects analysed              | 2864                     |  |  |  |
| Units: subjects                          |                          |  |  |  |
| number (not applicable)                  |                          |  |  |  |
| TEAEs                                    | 2847                     |  |  |  |
| TESAEs                                   | 1251                     |  |  |  |
| TEAEs leading to discontinuation of drug | 720                      |  |  |  |
| Drug related TEAEs                       | 2613                     |  |  |  |
| Subjects who died (Grade 5 TEAEs)        | 404                      |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Treatment-emergent High Laboratory Abnormalities (TELA)

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Treatment-emergent High Laboratory Abnormalities (TELA) <sup>[2]</sup> |
|-----------------|--|

End point description:

A TELA was any abnormal event arising after the start of study drug administration, which focused on coagulation, general chemistry, hematology, hormone panels and thyroid function test. The denominator (D) represents the number of subjects at baseline with a normal or lower than normal laboratory assessment (LA) who also had at least one valid laboratory value after start of treatment. Subjects with missing or high abnormal values at baseline are not included in the D. The numerator represents the number of subjects with at least one high LA after the start of treatment who had a normal or lower than normal LA at baseline. If there are repeated observations prior to first study drug intake, baseline is defined as the last non-missing pre-treatment measurement, where baseline cannot be set on the same date as the first study drug intake. SAF, number of subjects analyzed signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of study treatment up to 14 days after the last dose of study drug

Notes:

[2] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                               | Regorafenib (BAY73-4506) |  |  |  |
|--|--------------------------|--|--|--|
| Subject group type                             | Reporting group          |  |  |  |
| Number of subjects analysed                    | 2864                     |  |  |  |
| Units: percentage of subjects                  |                          |  |  |  |
| number (not applicable)                        |                          |  |  |  |
| Activated Partial Thromboplastin Time (n=1745) | 23.5                     |  |  |  |
| Prothrombin Intl. Normalized Ratio (n=1719)    | 20.9                     |  |  |  |
| Prothrombin Time (n=684)                       | 29.2                     |  |  |  |
| Alanine Aminotransferase (n=2049)              | 43.9                     |  |  |  |
| Alkaline Phosphatase (n=993)                   | 48.5                     |  |  |  |
| Aspartate Aminotransferase (n=1630)            | 61.4                     |  |  |  |
| Bilirubin (n=2290)                             | 58.1                     |  |  |  |
| Calcium (n=2266)                               | 3.5                      |  |  |  |
| Chloride (n=2225)                              | 11.2                     |  |  |  |
| Creatinine (n=2240)                            | 12.9                     |  |  |  |
| Direct Bilirubin (n=1368)                      | 61.9                     |  |  |  |
| Phosphate (n=2111)                             | 3.8                      |  |  |  |
| Potassium (n=2312)                             | 13.4                     |  |  |  |
| Sodium (n=2392)                                | 5                        |  |  |  |

|                                 |      |  |  |  |
|---------------------------------|------|--|--|--|
| Triacylglycerol Lipase (n=2138) | 37.6 |  |  |  |
| Basophils (n=1878)              | 5.6  |  |  |  |
| Basophils/Leukocytes (n=695)    | 8.2  |  |  |  |
| Eosinophils (n=1773)            | 13.7 |  |  |  |
| Eosinophils/Leukocytes (n=642)  | 20.7 |  |  |  |
| Erythrocytes (n=2374)           | 10.3 |  |  |  |
| Hematocrit (n=2394)             | 7.5  |  |  |  |
| Hemoglobin (n=2417)             | 5.3  |  |  |  |
| Leukocytes (n=2018)             | 36.6 |  |  |  |
| Lymphocytes (n=1941)            | 2.6  |  |  |  |
| Lymphocytes/Leukocytes (n=715)  | 2.5  |  |  |  |
| Monocytes (n=1593)              | 31.5 |  |  |  |
| Monocytes/Leukocytes (n=558)    | 35.1 |  |  |  |
| Neutrophils (n=1607)            | 38.1 |  |  |  |
| Neutrophils/Leukocytes (n=507)  | 49.7 |  |  |  |
| Platelets (n=2215)              | 15.4 |  |  |  |
| Thyrotropin (n=1805)            | 36.3 |  |  |  |
| Thyroxine, Free (n=1611)        | 9.8  |  |  |  |
| Triiodothyronine, Free (n=1382) | 4.1  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects With Treatment-emergent Low Laboratory Abnormalities (TELA)

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Treatment-emergent Low Laboratory Abnormalities (TELA) <sup>[3]</sup> |
|-----------------|---|

End point description:

A TELA was any abnormal event arising after the start of study drug administration, which focused on coagulation, general chemistry, hematology, hormone panels and thyroid function test. The D represents the number of subjects at baseline with a normal or higher than normal LA who also had at least one valid laboratory value after start of treatment. Subjects with missing or low abnormal values at baseline are not included in the D. The numerator represents the number of subjects with at least one low LA after the start of treatment who had a normal or higher than normal LA at baseline. If there are repeated observations prior to first study drug intake, baseline is defined as the last non-missing pre-treatment measurement, where baseline cannot be set on the same date as the first study drug intake. SAF, number of subjects analyzed signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of study treatment up to 14 days after the last dose of study drug

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                                  | Regorafenib<br>(BAY73-4506) |  |  |  |
|---|-----------------------------|--|--|--|
| Subject group type                                | Reporting group             |  |  |  |
| Number of subjects analysed                       | 2864                        |  |  |  |
| Units: percentage of subjects                     |                             |  |  |  |
| number (not applicable)                           |                             |  |  |  |
| Activated Partial Thromboplastin Time<br>(n=1905) | 7.8                         |  |  |  |
| Prothrombin Intl. Normalized Ratio<br>(n=1884)    | 1.8                         |  |  |  |
| Prothrombin Time (n=771)                          | 4.2                         |  |  |  |
| Alanine Aminotransferase (n=2402)                 | 4.1                         |  |  |  |
| Alkaline Phosphatase (n=2407)                     | 0.9                         |  |  |  |
| Aspartate Aminotransferase (n=2449)               | 1                           |  |  |  |
| Bilirubin (n=2437)                                | 1.2                         |  |  |  |
| Calcium (n=2226)                                  | 44.1                        |  |  |  |
| Chloride (n=2070)                                 | 29.9                        |  |  |  |
| Creatinine (n=2149)                               | 23.8                        |  |  |  |
| Direct Bilirubin (n=1736)                         | 0.2                         |  |  |  |
| Phosphate (n=2009)                                | 69.1                        |  |  |  |
| Potassium (n=2312)                                | 27.7                        |  |  |  |
| Sodium (n=2220)                                   | 36                          |  |  |  |
| Triacylglycerol Lipase (n=2150)                   | 7                           |  |  |  |
| Basophils (n=1879)                                | 2.4                         |  |  |  |
| Basophils/Leukocytes (n=701)                      | 2                           |  |  |  |
| Eosinophils (n=1849)                              | 10.3                        |  |  |  |
| Eosinophils/Leukocytes (n=636)                    | 18.9                        |  |  |  |
| Erythrocytes (n=1351)                             | 39.5                        |  |  |  |
| Hematocrit (n=1360)                               | 47.9                        |  |  |  |
| Hemoglobin (n=1262)                               | 44.9                        |  |  |  |
| Leukocytes (n=2343)                               | 13.2                        |  |  |  |
| Lymphocytes (n=1388)                              | 39.1                        |  |  |  |
| Lymphocytes/Leukocytes (n=369)                    | 56.1                        |  |  |  |
| Monocytes (n=1920)                                | 3.8                         |  |  |  |
| Monocytes/Leukocytes (n=714)                      | 7.4                         |  |  |  |
| Neutrophils (n=1968)                              | 5.9                         |  |  |  |
| Neutrophils/Leukocytes (n=714)                    | 3.8                         |  |  |  |
| Platelets (n=2169)                                | 30.1                        |  |  |  |
| Thyrotropin (n=1926)                              | 4.8                         |  |  |  |
| Thyroxine, Free (n=1644)                          | 4.9                         |  |  |  |
| Triiodothyronine, Free (n=1285)                   | 18.6                        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline in Heart Rate at Specified Time Points

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Heart Rate at Specified Time Points <sup>[4]</sup> |
|-----------------|--|

End point description:

SAF, Here "N" (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n"

signifies subjects evaluable for the specified category. In the below table 99999 represents as the sample size was not sufficient. Hence, Standard deviation was not calculated.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Day 1 (Cycle 1 to 33), and end of treatment

Notes:

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

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib<br>(BAY73-4506) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 2864                        |  |  |  |
| Units: beats per minute              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Cycle 1 Day 1 (n = 1067)             | -0.4 (± 10.8)               |  |  |  |
| Cycle 2 Day 1 (n = 1915)             | 2.4 (± 13)                  |  |  |  |
| Cycle 3 Day 1 (n = 1376)             | 1.8 (± 12.6)                |  |  |  |
| Cycle 4 Day 1 (n = 927)              | 1.4 (± 13.2)                |  |  |  |
| Cycle 5 Day 1 (n = 651)              | 1.4 (± 12.8)                |  |  |  |
| Cycle 6 Day 1 (n = 503)              | 1.1 (± 12.8)                |  |  |  |
| Cycle 7 Day 1 (n = 364)              | 0.9 (± 13.4)                |  |  |  |
| Cycle 8 Day 1 (n = 287)              | 0.4 (± 14)                  |  |  |  |
| Cycle 9 Day 1 (n = 234)              | 1 (± 13)                    |  |  |  |
| Cycle 10 Day 1 (n = 189)             | 1.2 (± 12.6)                |  |  |  |
| Cycle 11 Day 1 (n = 157)             | 0.2 (± 12.9)                |  |  |  |
| Cycle 12 Day 1 (n = 136)             | 1.1 (± 12.1)                |  |  |  |
| Cycle 13 Day 1 (n = 110)             | 1.4 (± 13.8)                |  |  |  |
| Cycle 14 Day 1 (n = 88)              | 1.3 (± 11.7)                |  |  |  |
| Cycle 15 Day 1 (n = 73)              | 1.3 (± 13.6)                |  |  |  |
| Cycle 16 Day 1 (n = 60)              | 0.2 (± 13.8)                |  |  |  |
| Cycle 17 Day 1 (n = 52)              | 1.4 (± 13.6)                |  |  |  |
| Cycle 18 Day 1 (n = 43)              | 0.4 (± 12.7)                |  |  |  |
| Cycle 19 Day 1 (n = 36)              | 1.2 (± 13.2)                |  |  |  |
| Cycle 20 Day 1 (n = 28)              | 3.7 (± 14.3)                |  |  |  |
| Cycle 21 Day 1 (n = 24)              | 3.9 (± 14.3)                |  |  |  |
| Cycle 22 Day 1 (n = 18)              | 2.7 (± 9.8)                 |  |  |  |
| Cycle 23 Day 1 (n = 15)              | -0.9 (± 13.4)               |  |  |  |
| Cycle 24 Day 1 (n = 11)              | -1.4 (± 11)                 |  |  |  |
| Cycle 25 Day 1 (n = 11)              | 0.9 (± 12.6)                |  |  |  |
| Cycle 26 Day 1 (n = 9)               | 2.6 (± 14.4)                |  |  |  |
| Cycle 27 Day 1 (n = 7)               | -3 (± 11.3)                 |  |  |  |
| Cycle 28 Day 1 (n = 7)               | 1.4 (± 14.5)                |  |  |  |
| Cycle 29 Day 1 (n = 5)               | -4.6 (± 12.2)               |  |  |  |
| Cycle 30 Day 1 (n = 3)               | -7.7 (± 14.2)               |  |  |  |
| Cycle 31 Day 1 (n = 1)               | 7 (± 99999)                 |  |  |  |
| Cycle 32 Day 1 (n = 1)               | 3 (± 99999)                 |  |  |  |
| Cycle 33 Day 1 (n = 1)               | -1 (± 99999)                |  |  |  |
| End of Treatment (n = 1468)          | 4.5 (± 14.6)                |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Diastolic Blood Pressure at Specified Time Points

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Diastolic Blood Pressure at Specified Time Points <sup>[5]</sup> |
|-----------------|--|

End point description:

SAF, Here "N" (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category. In the below table 99999 represents as the sample size was not sufficient. Hence, Standard deviation was not calculated.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Cycle 1 Days 1, 8, 15, 22; Cycle 2 Days 1, 8, 15; Cycle 3 to 33 (Day 1), and End of treatment

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib<br>(BAY73-4506) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 2864                        |  |  |  |
| Units: millimeter of mercury (mmHg)  |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Cycle 1 Day 1 (n=1096)               | -0.3 (± 7.8)                |  |  |  |
| Cycle 1 Day 8 (n=1896)               | 4.1 (± 11)                  |  |  |  |
| Cycle 1 Day 15 (n=2146)              | 3.6 (± 11.5)                |  |  |  |
| Cycle 1 Day 22 (n=1578)              | 2.4 (± 10.5)                |  |  |  |
| Cycle 2 Day 1 (n=1976)               | 0 (± 10.2)                  |  |  |  |
| Cycle 2 Day 8 (n=1343)               | 3.1 (± 11.2)                |  |  |  |
| Cycle 2 Day 15 (n=1724)              | 3.3 (± 10.5)                |  |  |  |
| Cycle 3 Day 1 (n=1412)               | -1.2 (± 10.2)               |  |  |  |
| Cycle 4 Day 1 (n=959)                | -1 (± 10.2)                 |  |  |  |
| Cycle 5 Day 1 (n=674)                | -1.5 (± 9.6)                |  |  |  |
| Cycle 6 Day 1 (n=527)                | -0.9 (± 10.4)               |  |  |  |
| Cycle 7 Day 1 (n=374)                | -1 (± 10.4)                 |  |  |  |
| Cycle 8 Day 1 (n=297)                | -1.7 (± 11.2)               |  |  |  |
| Cycle 9 Day 1 (n=248)                | -1.3 (± 10.3)               |  |  |  |
| Cycle 10 Day 1 (n=197)               | -0.8 (± 10.3)               |  |  |  |
| Cycle 11 Day 1 (n=163)               | -1 (± 10.3)                 |  |  |  |
| Cycle 12 Day 1 (n=143)               | -1.2 (± 10.6)               |  |  |  |
| Cycle 13 Day 1 (n=113)               | -1.9 (± 10.6)               |  |  |  |
| Cycle 14 Day 1 (n=92)                | -2.1 (± 9.9)                |  |  |  |
| Cycle 15 Day 1 (n=78)                | -1.6 (± 10.5)               |  |  |  |
| Cycle 16 Day 1 (n=63)                | -5.5 (± 10.7)               |  |  |  |
| Cycle 17 Day 1 (n=54)                | -2.7 (± 11)                 |  |  |  |

|                           |               |  |  |  |
|---------------------------|---------------|--|--|--|
| Cycle 18 Day 1 (n=44)     | -2.4 (± 11.7) |  |  |  |
| Cycle 19 Day 1 (n=36)     | -3.5 (± 12.2) |  |  |  |
| Cycle 20 Day 1 (n=29)     | -1.4 (± 10.5) |  |  |  |
| Cycle 21 Day 1 (n=24)     | -0.7 (± 12.4) |  |  |  |
| Cycle 22 Day 1 (n=18)     | -4.9 (± 13)   |  |  |  |
| Cycle 23 Day 1 (n=15)     | -4.4 (± 10.6) |  |  |  |
| Cycle 24 Day 1 (n=11)     | -3.1 (± 12.1) |  |  |  |
| Cycle 25 Day 1 (n=11)     | -6.7 (± 13)   |  |  |  |
| Cycle 26 Day 1 (n=9)      | -5.2 (± 9.5)  |  |  |  |
| Cycle 27 Day 1 (n=7)      | -3.6 (± 11)   |  |  |  |
| Cycle 28 Day 1 (n=7)      | -3.9 (± 13.2) |  |  |  |
| Cycle 29 Day 1 (n=5)      | -5.2 (± 10.4) |  |  |  |
| Cycle 30 Day 1 (n=3)      | -3.3 (± 7.6)  |  |  |  |
| Cycle 31 Day 1 (n=1)      | 6 (± 99999)   |  |  |  |
| Cycle 32 Day 1 (n=1)      | 6 (± 99999)   |  |  |  |
| Cycle 33 Day 1 (n=1)      | 4 (± 99999)   |  |  |  |
| End of Treatment (n=1520) | -0.9 (± 11.2) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Systolic Blood Pressure at Specified Time Points

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Systolic Blood Pressure at Specified Time Points <sup>[6]</sup> |
|-----------------|---|

End point description:

SAF, Here "N" (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category. In the below table 99999 represents as the sample size was not sufficient. Hence, Standard deviation was not calculated.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Cycle 1 Days 1, 8, 15, 22; Cycle 2 Days 1, 8, 15; Cycle 3 to 33 (Day 1), and End of treatment

Notes:

[6] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib (BAY73-4506) |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 2841                     |  |  |  |
| Units: millimeter of mercury (mmHg)  |                          |  |  |  |
| arithmetic mean (standard deviation) |                          |  |  |  |
| Cycle 1 Day 1 (n=1096)               | 0.4 (± 10.8)             |  |  |  |
| Cycle 1 Day 8 (n=1896)               | 6.4 (± 15.9)             |  |  |  |
| Cycle 1 Day 15 (n=2149)              | 5.7 (± 16.3)             |  |  |  |
| Cycle 1 Day 22 (n=1579)              | 3.6 (± 15.7)             |  |  |  |
| Cycle 2 Day 1 (n=1978)               | 0.6 (± 4.6)              |  |  |  |
| Cycle 2 Day 8 (n=1343)               | 5.4 (± 15.9)             |  |  |  |
| Cycle 2 Day 15 (n=1724)              | 4.8 (± 16.5)             |  |  |  |
| Cycle 3 Day 1 (n=1413)               | -1.1 (± 15.4)            |  |  |  |

|                           |               |  |  |  |
|---------------------------|---------------|--|--|--|
| Cycle 4 Day 1 (n=959)     | -0.9 (± 14.9) |  |  |  |
| Cycle 5 Day 1 (n=674)     | -1.3 (± 15.2) |  |  |  |
| Cycle 6 Day 1 (n=527)     | -1.1 (± 15.9) |  |  |  |
| Cycle 7 Day 1 (n=374)     | -0.5 (± 16)   |  |  |  |
| Cycle 8 Day 1 (n=297)     | -1.6 (± 15.8) |  |  |  |
| Cycle 9 Day 1 (n=248)     | -0.7 (± 14.9) |  |  |  |
| Cycle 10 Day 1 (n=197)    | -0.9 (± 15.6) |  |  |  |
| Cycle 11 Day 1 (n=163)    | -1.2 (± 14.5) |  |  |  |
| Cycle 12 Day 1 (n=143)    | 0.2 (± 15.3)  |  |  |  |
| Cycle 13 Day 1 (n=113)    | 1.1 (± 14.3)  |  |  |  |
| Cycle 14 Day 1 (n=92)     | -1.1 (± 18.1) |  |  |  |
| Cycle 15 Day 1 (n=78)     | 0.9 (± 14.5)  |  |  |  |
| Cycle 16 Day 1 (n=63)     | -2.8 (± 14.2) |  |  |  |
| Cycle 17 Day 1 (n=54)     | 1.1 (± 13.8)  |  |  |  |
| Cycle 18 Day 1 (n=44)     | -1 (± 14.3)   |  |  |  |
| Cycle 19 Day 1 (n=36)     | 0.1 (± 19.3)  |  |  |  |
| Cycle 20 Day 1 (n=29)     | 4.6 (± 16.6)  |  |  |  |
| Cycle 21 Day 1 (n=24)     | 2.5 (± 15.8)  |  |  |  |
| Cycle 22 Day 1 (n=18)     | 1.9 (± 14.6)  |  |  |  |
| Cycle 23 Day 1 (n=15)     | 0.1 (± 10.5)  |  |  |  |
| Cycle 24 Day 1 (n=11)     | 3.5 (± 19)    |  |  |  |
| Cycle 25 Day 1 (n=11)     | -1.6 (± 14.2) |  |  |  |
| Cycle 26 Day 1 (n=9)      | 6.8 (± 25)    |  |  |  |
| Cycle 27 Day 1 (n=7)      | 1.4 (± 18.4)  |  |  |  |
| Cycle 28 Day 1 (n=7)      | -0.3 (± 13.3) |  |  |  |
| Cycle 29 Day 1 (n=5)      | -2.2 (± 19.5) |  |  |  |
| Cycle 30 Day 1 (n=3)      | 3 (± 11.5)    |  |  |  |
| Cycle 31 Day 1 (n=1)      | 6 (± 99999)   |  |  |  |
| Cycle 32 Day 1 (n=1)      | 11 (± 99999)  |  |  |  |
| Cycle 33 Day 1 (n=1)      | 20 (± 99999)  |  |  |  |
| End of Treatment (n=1521) | -1.8 (± 16.1) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subject With Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at Specified Time Points

|                 |  |
|-----------------|--|
| End point title | Percentage of Subject With Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at Specified Time Points <sup>[7]</sup> |
|-----------------|--|

End point description:

ECOG PS score was measured in a scale of 0-5, where 0= Fully active, able to carry on all pre-disease performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed or chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care. Totally confined to bed or chair and, 5= Death. SAF, Here "N" (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Day 1 (Cycle 1 to 33), and End of treatment

Notes:

[7] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                  | Regorafenib<br>(BAY73-4506) |  |  |  |
|-----------------------------------|-----------------------------|--|--|--|
| Subject group type                | Reporting group             |  |  |  |
| Number of subjects analysed       | 2864                        |  |  |  |
| Units: percentage of subjects     |                             |  |  |  |
| number (not applicable)           |                             |  |  |  |
| Cycle 1 Day 1 (n=1553): Unchanged | 89.4                        |  |  |  |
| Cycle 1 Day 1 (n=1553): 0 to 1    | 6                           |  |  |  |
| Cycle 1 Day 1 (n=1553): 0 to 2    | 0                           |  |  |  |
| Cycle 1 Day 1 (n=1553): 0 to 3    | 0                           |  |  |  |
| Cycle 1 Day 1 (n=1553): 0 to 4    | 0                           |  |  |  |
| Cycle 1 Day 1 (n=1553): 1 to 0    | 4.3                         |  |  |  |
| Cycle 1 Day 1 (n=1553): 1 to 2    | 0.3                         |  |  |  |
| Cycle 1 Day 1 (n=1553): 1 to 3    | 0                           |  |  |  |
| Cycle 1 Day 1 (n=1553): 1 to 4    | 0                           |  |  |  |
| Cycle 1 Day 1 (n=1553): Missing   | 0.1                         |  |  |  |
| Cycle 2 Day 1 (n=2298): Unchanged | 71                          |  |  |  |
| Cycle 2 Day 1 (n=2298): 0 to 1    | 16.6                        |  |  |  |
| Cycle 2 Day 1 (n=2298): 0 to 2    | 1.3                         |  |  |  |
| Cycle 2 Day 1 (n=2298): 0 to 3    | 0                           |  |  |  |
| Cycle 2 Day 1 (n=2298): 0 to 4    | 0                           |  |  |  |
| Cycle 2 Day 1 (n=2298): 1 to 0    | 5                           |  |  |  |
| Cycle 2 Day 1 (n=2298): 1 to 2    | 5.4                         |  |  |  |
| Cycle 2 Day 1 (n=2298): 1 to 3    | 0.4                         |  |  |  |
| Cycle 2 Day 1 (n=2298): 1 to 4    | 0                           |  |  |  |
| Cycle 2 Day 1 (n=2298): Missing   | 0.2                         |  |  |  |
| Cycle 3 Day 1 (n=1616): Unchanged | 69.8                        |  |  |  |
| Cycle 3 Day 1 (n=1616): 0 to 1    | 19.5                        |  |  |  |
| Cycle 3 Day 1 (n=1616): 0 to 2    | 0.9                         |  |  |  |
| Cycle 3 Day 1 (n=1616): 0 to 3    | 0.2                         |  |  |  |
| Cycle 3 Day 1 (n=1616): 0 to 4    | 0                           |  |  |  |
| Cycle 3 Day 1 (n=1616): 1 to 0    | 5.3                         |  |  |  |
| Cycle 3 Day 1 (n=1616): 1 to 2    | 4.1                         |  |  |  |
| Cycle 3 Day 1 (n=1616): 1 to 3    | 0.1                         |  |  |  |
| Cycle 3 Day 1 (n=1616): 1 to 4    | 0                           |  |  |  |
| Cycle 3 Day 1 (n=1616): Missing   | 0.1                         |  |  |  |
| Cycle 4 Day 1 (n=1098): Unchanged | 69.9                        |  |  |  |
| Cycle 4 Day 1 (n=1098): 0 to 1    | 17.8                        |  |  |  |
| Cycle 4 Day 1 (n=1098): 0 to 2    | 1.3                         |  |  |  |
| Cycle 4 Day 1 (n=1098): 0 to 3    | 0                           |  |  |  |
| Cycle 4 Day 1 (n=1098): 0 to 4    | 0                           |  |  |  |
| Cycle 4 Day 1 (n=1098): 1 to 0    | 5.9                         |  |  |  |
| Cycle 4 Day 1 (n=1098): 1 to 2    | 4.6                         |  |  |  |
| Cycle 4 Day 1 (n=1098): 1 to 3    | 0.5                         |  |  |  |
| Cycle 4 Day 1 (n=1098): 1 to 4    | 0                           |  |  |  |



|                                   |      |  |  |  |
|-----------------------------------|------|--|--|--|
| Cycle 4 Day 1 (n=1098): Missing   | 0.2  |  |  |  |
| Cycle 5 Day 1 (n=769): Unchanged  | 68.4 |  |  |  |
| Cycle 5 Day 1 (n=769): 0 to 1     | 19.4 |  |  |  |
| Cycle 5 Day 1 (n=769): 0 to 2     | 1.3  |  |  |  |
| Cycle 5 Day 1 (n=769): 0 to 3     | 0    |  |  |  |
| Cycle 5 Day 1 (n=769): 0 to 4     | 0    |  |  |  |
| Cycle 5 Day 1 (n=769): 1 to 0     | 6.5  |  |  |  |
| Cycle 5 Day 1 (n=769): 1 to 2     | 4.3  |  |  |  |
| Cycle 5 Day 1 (n=769): 1 to 3     | 0.1  |  |  |  |
| Cycle 5 Day 1 (n=769): 1 to 4     | 0    |  |  |  |
| Cycle 6 Day 1 (n=599): Unchanged  | 68.8 |  |  |  |
| Cycle 6 Day 1 (n=599): 0 to 1     | 20   |  |  |  |
| Cycle 6 Day 1 (n=599): 0 to 2     | 0.8  |  |  |  |
| Cycle 6 Day 1 (n=599): 0 to 3     | 0    |  |  |  |
| Cycle 6 Day 1 (n=599): 0 to 4     | 0    |  |  |  |
| Cycle 6 Day 1 (n=599): 1 to 0     | 5.3  |  |  |  |
| Cycle 6 Day 1 (n=599): 1 to 2     | 4.7  |  |  |  |
| Cycle 6 Day 1 (n=599): 1 to 3     | 0.2  |  |  |  |
| Cycle 6 Day 1 (n=599): 1 to 4     | 0    |  |  |  |
| Cycle 6 Day 1 (n=599): Missing    | 0.2  |  |  |  |
| Cycle 7 Day 1 (n=422): Unchanged  | 70.1 |  |  |  |
| Cycle 7 Day 1 (n=422): 0 to 1     | 20.1 |  |  |  |
| Cycle 7 Day 1 (n=422): 0 to 2     | 0.5  |  |  |  |
| Cycle 7 Day 1 (n=422): 0 to 3     | 0    |  |  |  |
| Cycle 7 Day 1 (n=422): 0 to 4     | 0    |  |  |  |
| Cycle 7 Day 1 (n=422): 1 to 0     | 5.7  |  |  |  |
| Cycle 7 Day 1 (n=422): 1 to 2     | 3.3  |  |  |  |
| Cycle 7 Day 1 (n=422): 1 to 3     | 0.2  |  |  |  |
| Cycle 7 Day 1 (n=422): 1 to 4     | 0    |  |  |  |
| Cycle 8 Day 1 (n=332): Unchanged  | 69.3 |  |  |  |
| Cycle 8 Day 1 (n=332): 0 to 1     | 21.4 |  |  |  |
| Cycle 8 Day 1 (n=332): 0 to 2     | 0.9  |  |  |  |
| Cycle 8 Day 1 (n=332): 0 to 3     | 0.3  |  |  |  |
| Cycle 8 Day 1 (n=332): 0 to 4     | 0    |  |  |  |
| Cycle 8 Day 1 (n=332): 1 to 0     | 6    |  |  |  |
| Cycle 8 Day 1 (n=332): 1 to 2     | 2.1  |  |  |  |
| Cycle 8 Day 1 (n=332): 1 to 3     | 0    |  |  |  |
| Cycle 8 Day 1 (n=332): 1 to 4     | 0    |  |  |  |
| Cycle 9 Day 1 (n=278): Unchanged  | 67.3 |  |  |  |
| Cycle 9 Day 1 (n=278): 0 to 1     | 22.7 |  |  |  |
| Cycle 9 Day 1 (n=278): 0 to 2     | 0.7  |  |  |  |
| Cycle 9 Day 1 (n=278): 0 to 3     | 0    |  |  |  |
| Cycle 9 Day 1 (n=278): 0 to 4     | 0    |  |  |  |
| Cycle 9 Day 1 (n=278): 1 to 0     | 7.2  |  |  |  |
| Cycle 9 Day 1 (n=278): 1 to 2     | 1.4  |  |  |  |
| Cycle 9 Day 1 (n=278): 1 to 3     | 0.4  |  |  |  |
| Cycle 9 Day 1 (n=278): 1 to 4     | 0    |  |  |  |
| Cycle 9 Day 1 (n=278): Missing    | 0.4  |  |  |  |
| Cycle 10 Day 1 (n=221): Unchanged | 69.2 |  |  |  |
| Cycle 10 Day 1 (n=221): 0 to 1    | 21.3 |  |  |  |
| Cycle 10 Day 1 (n=221): 0 to 2    | 1.4  |  |  |  |
| Cycle 10 Day 1 (n=221): 0 to 3    | 0    |  |  |  |

|                                   |      |  |  |  |
|-----------------------------------|------|--|--|--|
| Cycle 10 Day 1 (n=221): 0 to 4    | 0    |  |  |  |
| Cycle 10 Day 1 (n=221): 1 to 0    | 6.3  |  |  |  |
| Cycle 10 Day 1 (n=221): 1 to 2    | 1.4  |  |  |  |
| Cycle 10 Day 1 (n=221): 1 to 3    | 0    |  |  |  |
| Cycle 10 Day 1 (n=221): 1 to 4    | 0    |  |  |  |
| Cycle 10 Day 1 (n=221): Missing   | 0.5  |  |  |  |
| Cycle 11 Day 1 (n=188): Unchanged | 63.3 |  |  |  |
| Cycle 11 Day 1 (n=188): 0 to 1    | 23.4 |  |  |  |
| Cycle 11 Day 1 (n=188): 0 to 2    | 2.1  |  |  |  |
| Cycle 11 Day 1 (n=188): 0 to 3    | 0    |  |  |  |
| Cycle 11 Day 1 (n=188): 0 to 4    | 0    |  |  |  |
| Cycle 11 Day 1 (n=188): 1 to 0    | 8    |  |  |  |
| Cycle 11 Day 1 (n=188): 1 to 2    | 2.7  |  |  |  |
| Cycle 11 Day 1 (n=188): 1 to 3    | 0.5  |  |  |  |
| Cycle 11 Day 1 (n=188): 1 to 4    | 0    |  |  |  |
| Cycle 12 Day 1 (n=159): Unchanged | 62.9 |  |  |  |
| Cycle 12 Day 1 (n=159): 0 to 1    | 25.8 |  |  |  |
| Cycle 12 Day 1 (n=159): 0 to 2    | 1.3  |  |  |  |
| Cycle 12 Day 1 (n=159): 0 to 3    | 0    |  |  |  |
| Cycle 12 Day 1 (n=159): 0 to 4    | 0    |  |  |  |
| Cycle 12 Day 1 (n=159): 1 to 0    | 6.3  |  |  |  |
| Cycle 12 Day 1 (n=159): 1 to 2    | 3.1  |  |  |  |
| Cycle 12 Day 1 (n=159): 1 to 3    | 0    |  |  |  |
| Cycle 12 Day 1 (n=159): 1 to 4    | 0    |  |  |  |
| Cycle 12 Day 1 (n=159): Missing   | 0.6  |  |  |  |
| Cycle 13 Day 1 (n=130): Unchanged | 68.5 |  |  |  |
| Cycle 13 Day 1 (n=130): 0 to 1    | 22.3 |  |  |  |
| Cycle 13 Day 1 (n=130): 0 to 2    | 0.8  |  |  |  |
| Cycle 13 Day 1 (n=130): 0 to 3    | 0.8  |  |  |  |
| Cycle 13 Day 1 (n=130): 0 to 4    | 0    |  |  |  |
| Cycle 13 Day 1 (n=130): 1 to 0    | 5.4  |  |  |  |
| Cycle 13 Day 1 (n=130): 1 to 2    | 1.5  |  |  |  |
| Cycle 13 Day 1 (n=130): 1 to 3    | 0    |  |  |  |
| Cycle 13 Day 1 (n=130): 1 to 4    | 0    |  |  |  |
| Cycle 13 Day 1 (n=130): Missing   | 0.8  |  |  |  |
| Cycle 14 Day 1 (n=105): Unchanged | 62.9 |  |  |  |
| Cycle 14 Day 1 (n=105): 0 to 1    | 27.6 |  |  |  |
| Cycle 14 Day 1 (n=105): 0 to 2    | 1.9  |  |  |  |
| Cycle 14 Day 1 (n=105): 0 to 3    | 0    |  |  |  |
| Cycle 14 Day 1 (n=105): 0 to 4    | 0    |  |  |  |
| Cycle 14 Day 1 (n=105): 1 to 0    | 5.7  |  |  |  |
| Cycle 14 Day 1 (n=105): 1 to 2    | 1    |  |  |  |
| Cycle 14 Day 1 (n=105): 1 to 3    | 0    |  |  |  |
| Cycle 14 Day 1 (n=105): 1 to 4    | 0    |  |  |  |
| Cycle 14 Day 1 (n=105): Missing   | 1    |  |  |  |
| Cycle 15 Day 1 (n=87): Unchanged  | 63.2 |  |  |  |
| Cycle 15 Day 1 (n=87): 0 to 1     | 26.4 |  |  |  |
| Cycle 15 Day 1 (n=87): 0 to 2     | 2.3  |  |  |  |
| Cycle 15 Day 1 (n=87): 0 to 3     | 0    |  |  |  |
| Cycle 15 Day 1 (n=87): 0 to 4     | 0    |  |  |  |
| Cycle 15 Day 1 (n=87): 1 to 0     | 6.9  |  |  |  |
| Cycle 15 Day 1 (n=87): 1 to 2     | 0    |  |  |  |

|                                  |      |  |  |  |
|----------------------------------|------|--|--|--|
| Cycle 15 Day 1 (n=87): 1 to 3    | 0    |  |  |  |
| Cycle 15 Day 1 (n=87): 1 to 4    | 0    |  |  |  |
| Cycle 15 Day 1 (n=87): Missing   | 1.1  |  |  |  |
| Cycle 16 Day 1 (n=69): Unchanged | 68.1 |  |  |  |
| Cycle 16 Day 1 (n=69): 0 to 1    | 21.7 |  |  |  |
| Cycle 16 Day 1 (n=69): 0 to 2    | 1.4  |  |  |  |
| Cycle 16 Day 1 (n=69): 0 to 3    | 0    |  |  |  |
| Cycle 16 Day 1 (n=69): 0 to 4    | 0    |  |  |  |
| Cycle 16 Day 1 (n=69): 1 to 0    | 5.8  |  |  |  |
| Cycle 16 Day 1 (n=69): 1 to 2    | 1.4  |  |  |  |
| Cycle 16 Day 1 (n=69): 1 to 3    | 0    |  |  |  |
| Cycle 16 Day 1 (n=69): 1 to 4    | 0    |  |  |  |
| Cycle 16 Day 1 (n=69): Missing   | 1.4  |  |  |  |
| Cycle 17 Day 1 (n=59): Unchanged | 69.5 |  |  |  |
| Cycle 17 Day 1 (n=59): 0 to 1    | 20.3 |  |  |  |
| Cycle 17 Day 1 (n=59): 0 to 2    | 3.4  |  |  |  |
| Cycle 17 Day 1 (n=59): 0 to 3    | 0    |  |  |  |
| Cycle 17 Day 1 (n=59): 0 to 4    | 0    |  |  |  |
| Cycle 17 Day 1 (n=59): 1 to 0    | 5.1  |  |  |  |
| Cycle 17 Day 1 (n=59): 1 to 2    | 1.7  |  |  |  |
| Cycle 17 Day 1 (n=59): 1 to 3    | 0    |  |  |  |
| Cycle 17 Day 1 (n=59): 1 to 4    | 0    |  |  |  |
| Cycle 18 Day 1 (n=47): Unchanged | 70.2 |  |  |  |
| Cycle 18 Day 1 (n=47): 0 to 1    | 17   |  |  |  |
| Cycle 18 Day 1 (n=47): 0 to 2    | 2.1  |  |  |  |
| Cycle 18 Day 1 (n=47): 0 to 3    | 0    |  |  |  |
| Cycle 18 Day 1 (n=47): 0 to 4    | 0    |  |  |  |
| Cycle 18 Day 1 (n=47): 1 to 0    | 8.5  |  |  |  |
| Cycle 18 Day 1 (n=47): 1 to 2    | 2.1  |  |  |  |
| Cycle 18 Day 1 (n=47): 1 to 3    | 0    |  |  |  |
| Cycle 18 Day 1 (n=47): 1 to 4    | 0    |  |  |  |
| Cycle 19 Day 1 (n=39): Unchanged | 76.9 |  |  |  |
| Cycle 19 Day 1 (n=39): 0 to 1    | 15.4 |  |  |  |
| Cycle 19 Day 1 (n=39): 0 to 2    | 2.6  |  |  |  |
| Cycle 19 Day 1 (n=39): 0 to 3    | 0    |  |  |  |
| Cycle 19 Day 1 (n=39): 0 to 4    | 0    |  |  |  |
| Cycle 19 Day 1 (n=39): 1 to 0    | 5.1  |  |  |  |
| Cycle 19 Day 1 (n=39): 1 to 2    | 0    |  |  |  |
| Cycle 19 Day 1 (n=39): 1 to 3    | 0    |  |  |  |
| Cycle 19 Day 1 (n=39): 1 to 4    | 0    |  |  |  |
| Cycle 20 Day 1 (n=31): Unchanged | 77.4 |  |  |  |
| Cycle 20 Day 1 (n=31): 0 to 1    | 16.1 |  |  |  |
| Cycle 20 Day 1 (n=31): 0 to 2    | 0    |  |  |  |
| Cycle 20 Day 1 (n=31): 0 to 3    | 0    |  |  |  |
| Cycle 20 Day 1 (n=31): 0 to 4    | 0    |  |  |  |
| Cycle 20 Day 1 (n=31): 1 to 0    | 6.5  |  |  |  |
| Cycle 20 Day 1 (n=31): 1 to 2    | 0    |  |  |  |
| Cycle 20 Day 1 (n=31): 1 to 3    | 0    |  |  |  |
| Cycle 20 Day 1 (n=31): 1 to 4    | 0    |  |  |  |
| Cycle 21 Day 1 (n=28): Unchanged | 75   |  |  |  |
| Cycle 21 Day 1 (n=28): 0 to 1    | 17.9 |  |  |  |
| Cycle 21 Day 1 (n=28): 0 to 2    | 3.6  |  |  |  |

|                                  |      |  |  |  |
|----------------------------------|------|--|--|--|
| Cycle 21 Day 1 (n=28): 0 to 3    | 0    |  |  |  |
| Cycle 21 Day 1 (n=28): 0 to 4    | 0    |  |  |  |
| Cycle 21 Day 1 (n=28): 1 to 0    | 3.6  |  |  |  |
| Cycle 21 Day 1 (n=28): 1 to 2    | 0    |  |  |  |
| Cycle 21 Day 1 (n=28): 1 to 3    | 0    |  |  |  |
| Cycle 21 Day 1 (n=28): 1 to 4    | 0    |  |  |  |
| Cycle 22 Day 1 (n=20): Unchanged | 75   |  |  |  |
| Cycle 22 Day 1 (n=20): 0 to 1    | 20   |  |  |  |
| Cycle 22 Day 1 (n=20): 0 to 2    | 0    |  |  |  |
| Cycle 22 Day 1 (n=20): 0 to 3    | 0    |  |  |  |
| Cycle 22 Day 1 (n=20): 0 to 4    | 0    |  |  |  |
| Cycle 22 Day 1 (n=20): 1 to 0    | 5    |  |  |  |
| Cycle 22 Day 1 (n=20): 1 to 2    | 0    |  |  |  |
| Cycle 22 Day 1 (n=20): 1 to 3    | 0    |  |  |  |
| Cycle 22 Day 1 (n=20): 1 to 4    | 0    |  |  |  |
| Cycle 23 Day 1 (n=16): Unchanged | 68.8 |  |  |  |
| Cycle 23 Day 1 (n=16): 0 to 1    | 25   |  |  |  |
| Cycle 23 Day 1 (n=16): 0 to 2    | 0    |  |  |  |
| Cycle 23 Day 1 (n=16): 0 to 3    | 0    |  |  |  |
| Cycle 23 Day 1 (n=16): 0 to 4    | 0    |  |  |  |
| Cycle 23 Day 1 (n=16): 1 to 0    | 6.3  |  |  |  |
| Cycle 23 Day 1 (n=16): 1 to 2    | 0    |  |  |  |
| Cycle 23 Day 1 (n=16): 1 to 3    | 0    |  |  |  |
| Cycle 23 Day 1 (n=16): 1 to 4    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): Unchanged | 75   |  |  |  |
| Cycle 24 Day 1 (n=12): 0 to 1    | 25   |  |  |  |
| Cycle 24 Day 1 (n=12): 0 to 2    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): 0 to 3    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): 0 to 4    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): 1 to 0    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): 1 to 2    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): 1 to 3    | 0    |  |  |  |
| Cycle 24 Day 1 (n=12): 1 to 4    | 0    |  |  |  |
| Cycle 25 Day 1 (n=11): Unchanged | 72.7 |  |  |  |
| Cycle 25 Day 1 (n=11): 0 to 1    | 18.2 |  |  |  |
| Cycle 25 Day 1 (n=11): 0 to 2    | 0    |  |  |  |
| Cycle 25 Day 1 (n=11): 0 to 3    | 0    |  |  |  |
| Cycle 25 Day 1 (n=11): 0 to 4    | 0    |  |  |  |
| Cycle 25 Day 1 (n=11): 1 to 0    | 9.1  |  |  |  |
| Cycle 25 Day 1 (n=11): 1 to 2    | 0    |  |  |  |
| Cycle 25 Day 1 (n=11): 1 to 3    | 0    |  |  |  |
| Cycle 25 Day 1 (n=11): 1 to 4    | 0    |  |  |  |
| Cycle 26 Day 1 (n=10): Unchanged | 60   |  |  |  |
| Cycle 26 Day 1 (n=10): 0 to 1    | 30   |  |  |  |
| Cycle 26 Day 1 (n=10): 0 to 2    | 0    |  |  |  |
| Cycle 26 Day 1 (n=10): 0 to 3    | 0    |  |  |  |
| Cycle 26 Day 1 (n=10): 0 to 4    | 0    |  |  |  |
| Cycle 26 Day 1 (n=10): 1 to 0    | 0    |  |  |  |
| Cycle 26 Day 1 (n=10): 1 to 2    | 0    |  |  |  |
| Cycle 26 Day 1 (n=10): 1 to 3    | 10   |  |  |  |
| Cycle 26 Day 1 (n=10): 1 to 4    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): Unchanged  | 62.5 |  |  |  |

|                                 |      |  |  |  |
|---------------------------------|------|--|--|--|
| Cycle 27 Day 1 (n=8): 0 to 1    | 37.5 |  |  |  |
| Cycle 27 Day 1 (n=8): 0 to 2    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): 0 to 3    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): 0 to 4    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): 1 to 0    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): 1 to 2    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): 1 to 3    | 0    |  |  |  |
| Cycle 27 Day 1 (n=8): 1 to 4    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): Unchanged | 50   |  |  |  |
| Cycle 28 Day 1 (n=8): 0 to 1    | 50   |  |  |  |
| Cycle 28 Day 1 (n=8): 0 to 2    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): 0 to 3    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): 0 to 4    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): 1 to 0    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): 1 to 2    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): 1 to 3    | 0    |  |  |  |
| Cycle 28 Day 1 (n=8): 1 to 4    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): Unchanged | 20   |  |  |  |
| Cycle 29 Day 1 (n=5): 0 to 1    | 80   |  |  |  |
| Cycle 29 Day 1 (n=5): 0 to 2    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): 0 to 3    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): 0 to 4    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): 1 to 0    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): 1 to 2    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): 1 to 3    | 0    |  |  |  |
| Cycle 29 Day 1 (n=5): 1 to 4    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): Unchanged | 66.7 |  |  |  |
| Cycle 30 Day 1 (n=3): 0 to 1    | 33.3 |  |  |  |
| Cycle 30 Day 1 (n=3): 0 to 2    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): 0 to 3    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): 0 to 4    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): 1 to 0    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): 1 to 2    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): 1 to 3    | 0    |  |  |  |
| Cycle 30 Day 1 (n=3): 1 to 4    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): Unchanged | 100  |  |  |  |
| Cycle 31 Day 1 (n=1): 0 to 1    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 0 to 2    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 0 to 3    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 0 to 4    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 1 to 0    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 1 to 2    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 1 to 3    | 0    |  |  |  |
| Cycle 31 Day 1 (n=1): 1 to 4    | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): Unchanged | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): 0 to 1    | 100  |  |  |  |
| Cycle 32 Day 1 (n=1): 0 to 2    | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): 0 to 3    | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): 0 to 4    | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): 1 to 0    | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): 1 to 2    | 0    |  |  |  |
| Cycle 32 Day 1 (n=1): 1 to 3    | 0    |  |  |  |

|                                      |      |  |  |  |
|--------------------------------------|------|--|--|--|
| Cycle 32 Day 1 (n=1): 1 to 4         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): Unchanged      | 100  |  |  |  |
| Cycle 33 Day 1 (n=1): 0 to 1         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 0 to 2         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 0 to 3         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 0 to 4         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 1 to 0         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 1 to 2         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 1 to 3         | 0    |  |  |  |
| Cycle 33 Day 1 (n=1): 1 to 4         | 0    |  |  |  |
| End of Treatment (n=1847): Unchanged | 43.5 |  |  |  |
| End of Treatment (n=1847): 0 to 1    | 21.6 |  |  |  |
| End of Treatment (n=1847): 0 to 2    | 7    |  |  |  |
| End of Treatment (n=1847): 0 to 3    | 2.4  |  |  |  |
| End of Treatment (n=1847): 0 to 4    | 0.2  |  |  |  |
| End of Treatment (n=1847): 1 to 0    | 2.2  |  |  |  |
| End of Treatment (n=1847): 1 to 2    | 13.5 |  |  |  |
| End of Treatment (n=1847): 1 to 3    | 8.6  |  |  |  |
| End of Treatment (n=1847): 1 to 4    | 0.8  |  |  |  |
| End of Treatment (n=1847): Missing   | 0.3  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Extent of Exposure - Number of Cycles Completed

|                 |  |
|-----------------|--|
| End point title | Extent of Exposure - Number of Cycles Completed <sup>[8]</sup> |
|-----------------|--|

End point description:

SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until 33 months

Notes:

[8] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Regorafenib<br>(BAY73-4506) |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 2862                        |  |  |  |
| Units: cycles                        |                             |  |  |  |
| arithmetic mean (standard deviation) | 4.1 (± 3.9)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Primary: Extent of Exposure - Treatment Duration in Weeks**

|                 |   |
|-----------------|---|
| End point title | Extent of Exposure - Treatment Duration in Weeks <sup>[9]</sup> |
|-----------------|---|

End point description:

Overall treatment duration in weeks including interruptions/delays and drug holidays was calculated as (Day of last dose minus day of first dose + 1) / 7. SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until 33 months

Notes:

[9] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib (BAY73-4506) |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 2864                     |  |  |  |
| Units: weeks                         |                          |  |  |  |
| arithmetic mean (standard deviation) | 15.4 (± 16.4)            |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Extent of Exposure - Treatment Duration for Actual Weeks Study Drug Received**

|                 |  |
|-----------------|--|
| End point title | Extent of Exposure - Treatment Duration for Actual Weeks Study Drug Received <sup>[10]</sup> |
|-----------------|--|

End point description:

Actual treatment duration in weeks excluding interruptions/delays and drug holidays was calculated as (Day of last dose minus day of first dose + 1) minus days of interruption and drug holidays / 7. SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until 33 months

Notes:

[10] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib (BAY73-4506) |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 2864                     |  |  |  |
| Units: weeks                         |                          |  |  |  |
| arithmetic mean (standard deviation) | 11 (± 11.4)              |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

### Primary: Extent of Exposure - Actual Daily Dose of Regorafenib

|  |   |
|--|---|
| End point title  | Extent of Exposure - Actual Daily Dose of Regorafenib <sup>[11]</sup> |
| End point description:<br>SAF, number of subjects analysed signifies subjects evaluable for this endpoint. |   |
| End point type   | Primary   |
| End point timeframe:<br>From start of study treatment until 33 months                                      |   |

Notes:

[11] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib<br>(BAY73-4506) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 2862                        |  |  |  |
| Units: milligram (mg)                |                             |  |  |  |
| arithmetic mean (standard deviation) | 145.8 (± 19.1)              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Extent of Exposure - Percent of Planned Dose Received

|  |   |
|--|---|
| End point title  | Extent of Exposure - Percent of Planned Dose Received <sup>[12]</sup> |
| End point description:<br>Planned dose describes the intended initial dose of the study drug. SAF, number of subjects analysed signifies subjects evaluable for this endpoint. |   |
| End point type   | Primary   |
| End point timeframe:<br>From start of study treatment until 33 months  |   |

Notes:

[12] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | Regorafenib<br>(BAY73-4506) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 2862                        |  |  |  |
| Units: percent of planned dose       |                             |  |  |  |
| arithmetic mean (standard deviation) | 75.1 (± 19.8)               |  |  |  |

### Statistical analyses



No statistical analyses for this end point

### Primary: Extent of Exposure - Percentage of Subjects With Total Amount of Dose Including Categories

|                 |  |
|-----------------|--|
| End point title | Extent of Exposure - Percentage of Subjects With Total Amount of Dose Including Categories <sup>[13]</sup> |
|-----------------|--|

End point description:

SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until 33 months

Notes:

[13] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values              | Regorafenib (BAY73-4506) |  |  |  |
|-------------------------------|--------------------------|--|--|--|
| Subject group type            | Reporting group          |  |  |  |
| Number of subjects analysed   | 2862                     |  |  |  |
| Units: percentage of subjects |                          |  |  |  |
| number (not applicable)       |                          |  |  |  |
| = <2000 mg                    | 7.9                      |  |  |  |
| >2000 to 5000 mg              | 21.6                     |  |  |  |
| >5000 to 8000 mg              | 23.2                     |  |  |  |
| >8000 to 11000 mg             | 16.2                     |  |  |  |
| >11000 mg                     | 31.1                     |  |  |  |
| Missing                       | 0.1                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Progression Free Survival (PFS)

|                 |   |
|-----------------|---|
| End point title | Progression Free Survival (PFS) <sup>[14]</sup> |
|-----------------|---|

End point description:

Progression-free survival was defined as the time from date of treatment assignment (i.e. date of first treatment) to date of first observed disease progression or death due to any cause, if death occurred while the subject was in the study (that is, by the last visit including during the safety follow-up visit date) and before progression was observed. Tumor measurements were made at intervals and with methods that complied with the institution's best standard of care. Full analysis set (FAS) included all subjects who were assigned to treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until 33 months

Notes:

[14] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

|                                  |                             |  |  |  |
|----------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>          | Regorafenib<br>(BAY73-4506) |  |  |  |
| Subject group type               | Reporting group             |  |  |  |
| Number of subjects analysed      | 2872                        |  |  |  |
| Units: days                      |                             |  |  |  |
| median (confidence interval 95%) | 81 (79 to 83)               |  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment up to 30 days after the last dose of study drug

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Regorafenib (BAY73-4506) |
|-----------------------|--------------------------|

Reporting group description:

Subjects received regorafenib 160 mg (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator's discretion.

| Serious adverse events  | Regorafenib (BAY73-4506) |  |  |
|---|--------------------------|--|--|
| Total subjects affected by serious adverse events                           |                          |  |  |
| subjects affected / exposed   | 1251 / 2864<br>(43.68%)  |  |  |
| number of deaths (all causes)   | 405                      |  |  |
| number of deaths resulting from adverse events                              |                          |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)         |                          |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other |                          |  |  |
| subjects affected / exposed   | 4 / 2864 (0.14%)         |  |  |
| occurrences causally related to treatment / all                             | 3 / 5                    |  |  |
| deaths causally related to treatment / all                                  | 0 / 0                    |  |  |
| Tumor pain  |                          |  |  |
| subjects affected / exposed   | 5 / 2864 (0.17%)         |  |  |
| occurrences causally related to treatment / all                             | 0 / 6                    |  |  |
| deaths causally related to treatment / all                                  | 0 / 0                    |  |  |
| Vascular disorders  |                          |  |  |
| Hematoma  |                          |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypotension                                     |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lymphedema                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypertension                                    |                   |  |  |
| subjects affected / exposed                     | 6 / 2864 (0.21%)  |  |  |
| occurrences causally related to treatment / all | 16 / 18           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vascular disorders - Other                      |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 2 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Peripheral ischemia                             |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Superior vena cava syndrome                     |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thromboembolic event                            |                   |  |  |
| subjects affected / exposed                     | 23 / 2864 (0.80%) |  |  |
| occurrences causally related to treatment / all | 11 / 27           |  |  |
| deaths causally related to treatment / all      | 1 / 1             |  |  |
| Vasculitis                                      |                   |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed                          | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Surgical and medical procedures                      |                   |  |  |
| Surgical and medical procedures - Other              |                   |  |  |
| subjects affected / exposed                          | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| General disorders and administration site conditions |                   |  |  |
| Death NOS  |                   |  |  |
| subjects affected / exposed                          | 8 / 2864 (0.28%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 8             |  |  |
| deaths causally related to treatment / all           | 1 / 8             |  |  |
| Edema limbs  |                   |  |  |
| subjects affected / exposed                          | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 4             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Fatigue  |                   |  |  |
| subjects affected / exposed                          | 27 / 2864 (0.94%) |  |  |
| occurrences causally related to treatment / all      | 21 / 30           |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Flu like symptoms                                    |                   |  |  |
| subjects affected / exposed                          | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Fever  |                   |  |  |
| subjects affected / exposed                          | 72 / 2864 (2.51%) |  |  |
| occurrences causally related to treatment / all      | 17 / 83           |  |  |
| deaths causally related to treatment / all           | 0 / 1             |  |  |
| Gait disturbance                                     |                   |  |  |
| subjects affected / exposed                          | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 2             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Localized edema  |                     |  |  |
| subjects affected / exposed                                  | 1 / 2864 (0.03%)    |  |  |
| occurrences causally related to treatment / all              | 0 / 1               |  |  |
| deaths causally related to treatment / all                   | 0 / 0               |  |  |
| Malaise  |                     |  |  |
| subjects affected / exposed                                  | 3 / 2864 (0.10%)    |  |  |
| occurrences causally related to treatment / all              | 0 / 3               |  |  |
| deaths causally related to treatment / all                   | 0 / 0               |  |  |
| Multi-organ failure  |                     |  |  |
| subjects affected / exposed                                  | 4 / 2864 (0.14%)    |  |  |
| occurrences causally related to treatment / all              | 0 / 5               |  |  |
| deaths causally related to treatment / all                   | 0 / 4               |  |  |
| General disorders and administration site conditions - Other |                     |  |  |
| subjects affected / exposed                                  | 328 / 2864 (11.45%) |  |  |
| occurrences causally related to treatment / all              | 23 / 497            |  |  |
| deaths causally related to treatment / all                   | 3 / 238             |  |  |
| Non-cardiac chest pain                                       |                     |  |  |
| subjects affected / exposed                                  | 13 / 2864 (0.45%)   |  |  |
| occurrences causally related to treatment / all              | 0 / 14              |  |  |
| deaths causally related to treatment / all                   | 0 / 0               |  |  |
| Sudden death NOS   |                     |  |  |
| subjects affected / exposed                                  | 1 / 2864 (0.03%)    |  |  |
| occurrences causally related to treatment / all              | 0 / 1               |  |  |
| deaths causally related to treatment / all                   | 0 / 1               |  |  |
| Pain   |                     |  |  |
| subjects affected / exposed                                  | 10 / 2864 (0.35%)   |  |  |
| occurrences causally related to treatment / all              | 0 / 13              |  |  |
| deaths causally related to treatment / all                   | 0 / 0               |  |  |
| Immune system disorders                                      |                     |  |  |
| Allergic reaction  |                     |  |  |
| subjects affected / exposed                                  | 4 / 2864 (0.14%)    |  |  |
| occurrences causally related to treatment / all              | 3 / 4               |  |  |
| deaths causally related to treatment / all                   | 0 / 0               |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| Reproductive system and breast disorders         |                  |  |  |
| Female genital tract fistula                     |                  |  |  |
| subjects affected / exposed                      | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1            |  |  |
| deaths causally related to treatment / all       | 0 / 0            |  |  |
| Reproductive system and breast disorders - Other |                  |  |  |
| subjects affected / exposed                      | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1            |  |  |
| deaths causally related to treatment / all       | 0 / 0            |  |  |
| Uterine hemorrhage                               |                  |  |  |
| subjects affected / exposed                      | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1            |  |  |
| deaths causally related to treatment / all       | 0 / 0            |  |  |
| Prostatic obstruction                            |                  |  |  |
| subjects affected / exposed                      | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1            |  |  |
| deaths causally related to treatment / all       | 0 / 0            |  |  |
| Vaginal fistula                                  |                  |  |  |
| subjects affected / exposed                      | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all  | 0 / 2            |  |  |
| deaths causally related to treatment / all       | 0 / 0            |  |  |
| Pelvic pain                                      |                  |  |  |
| subjects affected / exposed                      | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all  | 0 / 4            |  |  |
| deaths causally related to treatment / all       | 0 / 0            |  |  |
| Vaginal hemorrhage                               |                  |  |  |
| subjects affected / exposed                      | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all  | 0 / 4            |  |  |
| deaths causally related to treatment / all       | 0 / 1            |  |  |
| Respiratory, thoracic and mediastinal disorders  |                  |  |  |
| Adult respiratory distress syndrome              |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Aspiration                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Atelectasis                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Bronchopulmonary hemorrhage                     |                   |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 3 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Bronchial obstruction                           |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cough   |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dyspnea   |                   |  |  |
| subjects affected / exposed                     | 37 / 2864 (1.29%) |  |  |
| occurrences causally related to treatment / all | 1 / 55            |  |  |
| deaths causally related to treatment / all      | 0 / 13            |  |  |
| Epistaxis                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypoxia   |                   |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Hiccups   |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pleural effusion                                |                   |  |  |
| subjects affected / exposed                     | 27 / 2864 (0.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 38            |  |  |
| deaths causally related to treatment / all      | 0 / 3             |  |  |
| Pleuritic pain                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pneumonitis                                     |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Pneumothorax                                    |                   |  |  |
| subjects affected / exposed                     | 11 / 2864 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 13            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Pulmonary edema                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Respiratory failure                             |                   |  |  |
| subjects affected / exposed                     | 17 / 2864 (0.59%) |  |  |
| occurrences causally related to treatment / all | 0 / 26            |  |  |
| deaths causally related to treatment / all      | 0 / 15            |  |  |
| Voice alteration                                |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Psychiatric disorders                           |                   |  |  |
| Confusion                                       |                   |  |  |
| subjects affected / exposed                     | 13 / 2864 (0.45%) |  |  |
| occurrences causally related to treatment / all | 2 / 14            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anxiety   |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Delirium  |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 3 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Depression                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hallucinations                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Suicide attempt                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Psychosis                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Investigations                                  |                   |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| Alanine aminotransferase increased              |                   |  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |  |
| occurrences causally related to treatment / all | 6 / 8             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Aspartate aminotransferase increased            |                   |  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |  |
| occurrences causally related to treatment / all | 4 / 6             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Blood bilirubin increased                       |                   |  |  |  |
| subjects affected / exposed                     | 35 / 2864 (1.22%) |  |  |  |
| occurrences causally related to treatment / all | 13 / 51           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Cardiac troponin I increased                    |                   |  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| GGT increased                                   |                   |  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| INR increased                                   |                   |  |  |  |
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |  |
| occurrences causally related to treatment / all | 4 / 6             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Neutrophil count decreased                      |                   |  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Platelet count decreased                        |                   |  |  |  |
| subjects affected / exposed                     | 9 / 2864 (0.31%)  |  |  |  |
| occurrences causally related to treatment / all | 20 / 21           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Investigations - Other                          |                   |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                       | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all   | 1 / 2            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Electrocardiogram QT corrected interval prolonged |                  |  |  |
| subjects affected / exposed                       | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all   | 2 / 3            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Weight loss                                       |                  |  |  |
| subjects affected / exposed                       | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all   | 0 / 3            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| White blood cell decreased                        |                  |  |  |
| subjects affected / exposed                       | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Injury, poisoning and procedural complications    |                  |  |  |
| Burn  |                  |  |  |
| subjects affected / exposed                       | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Fall  |                  |  |  |
| subjects affected / exposed                       | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all   | 0 / 2            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Fracture  |                  |  |  |
| subjects affected / exposed                       | 8 / 2864 (0.28%) |  |  |
| occurrences causally related to treatment / all   | 0 / 8            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Hip fracture                                      |                  |  |  |
| subjects affected / exposed                       | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all   | 0 / 2            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Intestinal stoma site bleeding                    |                  |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed                            | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all        | 1 / 4            |  |  |
| deaths causally related to treatment / all             | 0 / 1            |  |  |
| Intestinal stoma leak                                  |                  |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1            |  |  |
| deaths causally related to treatment / all             | 0 / 0            |  |  |
| Injury, poisoning and procedural complications - Other |                  |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1            |  |  |
| deaths causally related to treatment / all             | 0 / 0            |  |  |
| Intestinal stoma obstruction                           |                  |  |  |
| subjects affected / exposed                            | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all        | 0 / 4            |  |  |
| deaths causally related to treatment / all             | 0 / 1            |  |  |
| Spinal fracture  |                  |  |  |
| subjects affected / exposed                            | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all        | 0 / 4            |  |  |
| deaths causally related to treatment / all             | 0 / 0            |  |  |
| Wound dehiscence                                       |                  |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1            |  |  |
| deaths causally related to treatment / all             | 0 / 0            |  |  |
| Wound complication                                     |                  |  |  |
| subjects affected / exposed                            | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all        | 0 / 3            |  |  |
| deaths causally related to treatment / all             | 0 / 0            |  |  |
| Cardiac disorders                                      |                  |  |  |
| Atrioventricular block first degree                    |                  |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1            |  |  |
| deaths causally related to treatment / all             | 0 / 0            |  |  |
| Atrioventricular block complete                        |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Acute coronary syndrome                         |                  |  |  |
| subjects affected / exposed                     | 8 / 2864 (0.28%) |  |  |
| occurrences causally related to treatment / all | 3 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Atrial fibrillation                             |                  |  |  |
| subjects affected / exposed                     | 9 / 2864 (0.31%) |  |  |
| occurrences causally related to treatment / all | 1 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Atrial flutter                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac arrest                                  |                  |  |  |
| subjects affected / exposed                     | 8 / 2864 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 8            |  |  |
| deaths causally related to treatment / all      | 1 / 8            |  |  |
| Heart failure                                   |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Chest pain - cardiac                            |                  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myocardial infarction                           |                  |  |  |
| subjects affected / exposed                     | 7 / 2864 (0.24%) |  |  |
| occurrences causally related to treatment / all | 3 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Cardiac disorders - Other                       |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pericarditis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pericardial effusion                            |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sinus bradycardia                               |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Supraventricular tachycardia                    |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ventricular tachycardia                         |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nervous system disorders                        |                  |  |  |
| Ataxia  |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cognitive disturbance                           |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dizziness                                       |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Depressed level of consciousness                |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Dysesthesia                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Encephalopathy                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Edema cerebral                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Headache  |                  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intracranial hemorrhage                         |                  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 1 / 2            |  |  |
| Facial nerve disorder                           |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ischemia cerebrovascular                        |                  |  |  |



|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Memory impairment                               |                   |  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Peripheral motor neuropathy                     |                   |  |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Neuralgia                                       |                   |  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Nervous system disorders - Other                |                   |  |  |  |
| subjects affected / exposed                     | 11 / 2864 (0.38%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 12            |  |  |  |
| deaths causally related to treatment / all      | 0 / 2             |  |  |  |
| Radiculitis                                     |                   |  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Peripheral sensory neuropathy                   |                   |  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Seizure   |                   |  |  |  |
| subjects affected / exposed                     | 10 / 2864 (0.35%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Somnolence                                      |                   |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Syncope   |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Stroke  |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Transient ischemic attacks                      |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blood and lymphatic system disorders            |                   |  |  |
| Anemia  |                   |  |  |
| subjects affected / exposed                     | 15 / 2864 (0.52%) |  |  |
| occurrences causally related to treatment / all | 8 / 23            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hemolysis                                       |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Febrile neutropenia                             |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blood and lymphatic system disorders - Other    |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ear and labyrinth disorders                     |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| Vestibular disorder                             |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Eye disorders                                   |                   |  |  |
| Corneal ulcer                                   |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal disorders                      |                   |  |  |
| Abdominal distension                            |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anal hemorrhage                                 |                   |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 2 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Abdominal pain                                  |                   |  |  |
| subjects affected / exposed                     | 65 / 2864 (2.27%) |  |  |
| occurrences causally related to treatment / all | 2 / 78            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anal fistula                                    |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ascites   |                   |  |  |
| subjects affected / exposed                     | 26 / 2864 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 34            |  |  |
| deaths causally related to treatment / all      | 0 / 5             |  |  |
| Colonic hemorrhage                              |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| Colonic fistula                                 |                   |  |  |  |
| subjects affected / exposed                     | 6 / 2864 (0.21%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 7             |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Colonic obstruction                             |                   |  |  |  |
| subjects affected / exposed                     | 29 / 2864 (1.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 37            |  |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |  |
| Colonic stenosis                                |                   |  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Colonic perforation                             |                   |  |  |  |
| subjects affected / exposed                     | 11 / 2864 (0.38%) |  |  |  |
| occurrences causally related to treatment / all | 4 / 14            |  |  |  |
| deaths causally related to treatment / all      | 1 / 3             |  |  |  |
| Duodenal hemorrhage                             |                   |  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Colitis   |                   |  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Duodenal obstruction                            |                   |  |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Constipation                                    |                   |  |  |  |
| subjects affected / exposed                     | 13 / 2864 (0.45%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 14            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Duodenal ulcer                                  |                   |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diarrhea  |                   |  |  |
| subjects affected / exposed                     | 29 / 2864 (1.01%) |  |  |
| occurrences causally related to treatment / all | 26 / 34           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dysphagia                                       |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dyspepsia                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Enterocolitis                                   |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Esophagitis                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Esophageal hemorrhage                           |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Enterovesical fistula                           |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Esophageal ulcer                                |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Esophageal varices hemorrhage                   |                   |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 1 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastritis                                       |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastric perforation                             |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal fistula                        |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastric hemorrhage                              |                   |  |  |
| subjects affected / exposed                     | 7 / 2864 (0.24%)  |  |  |
| occurrences causally related to treatment / all | 4 / 8             |  |  |
| deaths causally related to treatment / all      | 1 / 2             |  |  |
| Gastric stenosis                                |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ileus   |                   |  |  |
| subjects affected / exposed                     | 14 / 2864 (0.49%) |  |  |
| occurrences causally related to treatment / all | 1 / 17            |  |  |
| deaths causally related to treatment / all      | 0 / 2             |  |  |
| Ileal fistula                                   |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all | 2 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileal perforation                               |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileal obstruction                               |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Ileal stenosis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Jejunal obstruction                             |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Jejunal perforation                             |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Jejunal fistula                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lower gastrointestinal hemorrhage               |                  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mucositis oral                                  |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 7 / 2864 (0.24%) |  |  |
| occurrences causally related to treatment / all | 6 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nausea  |                  |  |  |
| subjects affected / exposed                     | 9 / 2864 (0.31%) |  |  |
| occurrences causally related to treatment / all | 3 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oral pain                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Obstruction gastric                             |                  |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders - Other              |                  |  |  |
| subjects affected / exposed                     | 8 / 2864 (0.28%) |  |  |
| occurrences causally related to treatment / all | 2 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis                                    |                  |  |  |
| subjects affected / exposed                     | 6 / 2864 (0.21%) |  |  |
| occurrences causally related to treatment / all | 4 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Proctitis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rectal fistula                                  |                  |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rectal hemorrhage                               |                  |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 10 / 2864 (0.35%) |  |  |
| occurrences causally related to treatment / all | 2 / 12            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Rectal obstruction                              |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Retroperitoneal hemorrhage                      |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Rectal perforation                              |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Small intestinal perforation                    |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Small intestinal obstruction                    |                   |  |  |
| subjects affected / exposed                     | 40 / 2864 (1.40%) |  |  |
| occurrences causally related to treatment / all | 2 / 51            |  |  |
| deaths causally related to treatment / all      | 0 / 6             |  |  |
| Upper gastrointestinal hemorrhage               |                   |  |  |
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 2 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vomiting  |                   |  |  |
| subjects affected / exposed                     | 19 / 2864 (0.66%) |  |  |
| occurrences causally related to treatment / all | 10 / 21           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatobiliary disorders                         |                   |  |  |
| Bile duct stenosis                              |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 31 / 2864 (1.08%) |  |  |
| occurrences causally related to treatment / all | 4 / 38            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cholecystitis                                   |                   |  |  |
| subjects affected / exposed                     | 10 / 2864 (0.35%) |  |  |
| occurrences causally related to treatment / all | 1 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Gallbladder obstruction                         |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatic failure                                 |                   |  |  |
| subjects affected / exposed                     | 35 / 2864 (1.22%) |  |  |
| occurrences causally related to treatment / all | 5 / 59            |  |  |
| deaths causally related to treatment / all      | 1 / 24            |  |  |
| Hepatic pain                                    |                   |  |  |
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Perforation bile duct                           |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatobiliary disorders - Other                 |                   |  |  |
| subjects affected / exposed                     | 6 / 2864 (0.21%)  |  |  |
| occurrences causally related to treatment / all | 1 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Portal vein thrombosis                          |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Skin and subcutaneous tissue disorders          |                   |  |  |
| Skin and subcutaneous tissue disorders - Other  |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Rash acneiform                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Palmar-plantar erythrodysesthesia syndrome      |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 3 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Rash maculo-papular                             |                   |  |  |
| subjects affected / exposed                     | 22 / 2864 (0.77%) |  |  |
| occurrences causally related to treatment / all | 28 / 29           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Toxic epidermal necrolysis                      |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Skin ulceration                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Urticaria                                       |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal and urinary disorders                     |                   |  |  |
| Acute kidney injury                             |                   |  |  |
| subjects affected / exposed                     | 27 / 2864 (0.94%) |  |  |
| occurrences causally related to treatment / all | 4 / 33            |  |  |
| deaths causally related to treatment / all      | 0 / 7             |  |  |
| Renal and urinary disorders - Other             |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 4 / 2864 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cystitis noninfective                           |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal hemorrhage                                |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hematuria                                       |                  |  |  |
| subjects affected / exposed                     | 6 / 2864 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary retention                               |                  |  |  |
| subjects affected / exposed                     | 8 / 2864 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract obstruction                       |                  |  |  |
| subjects affected / exposed                     | 9 / 2864 (0.31%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract pain                              |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endocrine disorders                             |                  |  |  |
| Hypothyroidism                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperthyroidism                                 |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Endocrine disorders - Other                     |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 30 / 2864 (1.05%) |  |  |
| occurrences causally related to treatment / all | 0 / 37            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bone pain                                       |                   |  |  |
| subjects affected / exposed                     | 7 / 2864 (0.24%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Generalized muscle weakness                     |                   |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 1 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Chest wall pain                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neck pain                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pain in extremity                               |                   |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed                            | 6 / 2864 (0.21%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 6             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Musculoskeletal and connective tissue disorder - Other |                   |  |  |
| subjects affected / exposed                            | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 2             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Pelvic soft tissue necrosis                            |                   |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 1             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Muscle weakness lower limb                             |                   |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 1             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Muscle weakness right-sided                            |                   |  |  |
| subjects affected / exposed                            | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 1             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Infections and infestations                            |                   |  |  |
| Anorectal infection                                    |                   |  |  |
| subjects affected / exposed                            | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all        | 1 / 5             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Abdominal infection                                    |                   |  |  |
| subjects affected / exposed                            | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all        | 1 / 5             |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Biliary tract infection                                |                   |  |  |
| subjects affected / exposed                            | 15 / 2864 (0.52%) |  |  |
| occurrences causally related to treatment / all        | 1 / 15            |  |  |
| deaths causally related to treatment / all             | 0 / 0             |  |  |
| Bronchial infection                                    |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Catheter related infection                      |                   |  |  |
| subjects affected / exposed                     | 8 / 2864 (0.28%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Device related infection                        |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Esophageal infection                            |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Duodenal infection                              |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Enterocolitis infectious                        |                   |  |  |
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 1 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatic infection                               |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lung infection                                  |                   |  |  |
| subjects affected / exposed                     | 54 / 2864 (1.89%) |  |  |
| occurrences causally related to treatment / all | 3 / 73            |  |  |
| deaths causally related to treatment / all      | 0 / 11            |  |  |
| Kidney infection                                |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Infective myositis                              |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Infections and infestations - Other             |                   |  |  |
| subjects affected / exposed                     | 21 / 2864 (0.73%) |  |  |
| occurrences causally related to treatment / all | 2 / 22            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Papulopustular rash                             |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peritoneal infection                            |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Otitis externa                                  |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pleural infection                               |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pelvic infection                                |                   |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Scrotal infection                               |                   |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Sepsis  |                   |  |  |
| subjects affected / exposed                     | 40 / 2864 (1.40%) |  |  |
| occurrences causally related to treatment / all | 6 / 52            |  |  |
| deaths causally related to treatment / all      | 2 / 13            |  |  |
| Skin infection                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 2864 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Soft tissue infection                           |                   |  |  |
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Upper respiratory infection                     |                   |  |  |
| subjects affected / exposed                     | 5 / 2864 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Urinary tract infection                         |                   |  |  |
| subjects affected / exposed                     | 27 / 2864 (0.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 29            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Wound infection                                 |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Metabolism and nutrition disorders              |                   |  |  |
| Acidosis  |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anorexia  |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 7 / 2864 (0.24%)  |  |  |
| occurrences causally related to treatment / all | 3 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypocalcemia                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dehydration                                     |                   |  |  |
| subjects affected / exposed                     | 24 / 2864 (0.84%) |  |  |
| occurrences causally related to treatment / all | 8 / 27            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Hypoglycemia                                    |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypokalemia                                     |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypophosphatemia                                |                   |  |  |
| subjects affected / exposed                     | 3 / 2864 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 11 / 12           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hyponatremia                                    |                   |  |  |
| subjects affected / exposed                     | 6 / 2864 (0.21%)  |  |  |
| occurrences causally related to treatment / all | 2 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hyperkalemia                                    |                   |  |  |
| subjects affected / exposed                     | 4 / 2864 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 2 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hyperglycemia                                   |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 2864 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metabolism and nutrition disorders - Other      |                  |  |  |
| subjects affected / exposed                     | 1 / 2864 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

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

|  |                          |  |  |
|--|--------------------------|--|--|
| <b>Non-serious adverse events</b>                            | Regorafenib (BAY73-4506) |  |  |
| Total subjects affected by non-serious adverse events        |                          |  |  |
| subjects affected / exposed                                  | 2785 / 2864 (97.24%)     |  |  |
| Vascular disorders   |                          |  |  |
| Hypertension   |                          |  |  |
| subjects affected / exposed                                  | 995 / 2864 (34.74%)      |  |  |
| occurrences (all)  | 2549                     |  |  |
| General disorders and administration site conditions         |                          |  |  |
| Edema limbs  |                          |  |  |
| subjects affected / exposed                                  | 153 / 2864 (5.34%)       |  |  |
| occurrences (all)  | 179                      |  |  |
| Fever  |                          |  |  |
| subjects affected / exposed                                  | 566 / 2864 (19.76%)      |  |  |
| occurrences (all)  | 761                      |  |  |
| Fatigue  |                          |  |  |
| subjects affected / exposed                                  | 1725 / 2864 (60.23%)     |  |  |
| occurrences (all)  | 3217                     |  |  |
| General disorders and administration site conditions - Other |                          |  |  |
| subjects affected / exposed                                  | 167 / 2864 (5.83%)       |  |  |
| occurrences (all)  | 198                      |  |  |
| Pain   |                          |  |  |
| subjects affected / exposed                                  | 344 / 2864 (12.01%)      |  |  |
| occurrences (all)  | 508                      |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                     |  |  |
| Cough   |                     |  |  |
| subjects affected / exposed                     | 226 / 2864 (7.89%)  |  |  |
| occurrences (all)                               | 260                 |  |  |
| Dyspnea   |                     |  |  |
| subjects affected / exposed                     | 370 / 2864 (12.92%) |  |  |
| occurrences (all)                               | 475                 |  |  |
| Hoarseness                                      |                     |  |  |
| subjects affected / exposed                     | 424 / 2864 (14.80%) |  |  |
| occurrences (all)                               | 508                 |  |  |
| Voice alteration                                |                     |  |  |
| subjects affected / exposed                     | 373 / 2864 (13.02%) |  |  |
| occurrences (all)                               | 482                 |  |  |
| Psychiatric disorders                           |                     |  |  |
| Insomnia  |                     |  |  |
| subjects affected / exposed                     | 149 / 2864 (5.20%)  |  |  |
| occurrences (all)                               | 163                 |  |  |
| Investigations                                  |                     |  |  |
| Alanine aminotransferase increased              |                     |  |  |
| subjects affected / exposed                     | 269 / 2864 (9.39%)  |  |  |
| occurrences (all)                               | 497                 |  |  |
| Alkaline phosphatase increased                  |                     |  |  |
| subjects affected / exposed                     | 189 / 2864 (6.60%)  |  |  |
| occurrences (all)                               | 255                 |  |  |
| Aspartate aminotransferase increased            |                     |  |  |
| subjects affected / exposed                     | 330 / 2864 (11.52%) |  |  |
| occurrences (all)                               | 567                 |  |  |
| Lipase increased                                |                     |  |  |
| subjects affected / exposed                     | 242 / 2864 (8.45%)  |  |  |
| occurrences (all)                               | 525                 |  |  |
| Blood bilirubin increased                       |                     |  |  |
| subjects affected / exposed                     | 604 / 2864 (21.09%) |  |  |
| occurrences (all)                               | 1306                |  |  |
| Weight loss                                     |                     |  |  |

|                                      |                        |  |  |
|--------------------------------------|------------------------|--|--|
| subjects affected / exposed          | 872 / 2864<br>(30.45%) |  |  |
| occurrences (all)                    | 1135                   |  |  |
| Platelet count decreased             |                        |  |  |
| subjects affected / exposed          | 225 / 2864 (7.86%)     |  |  |
| occurrences (all)                    | 339                    |  |  |
| Nervous system disorders             |                        |  |  |
| Headache                             |                        |  |  |
| subjects affected / exposed          | 296 / 2864<br>(10.34%) |  |  |
| occurrences (all)                    | 375                    |  |  |
| Blood and lymphatic system disorders |                        |  |  |
| Anemia                               |                        |  |  |
| subjects affected / exposed          | 308 / 2864<br>(10.75%) |  |  |
| occurrences (all)                    | 586                    |  |  |
| Gastrointestinal disorders           |                        |  |  |
| Abdominal pain                       |                        |  |  |
| subjects affected / exposed          | 561 / 2864<br>(19.59%) |  |  |
| occurrences (all)                    | 777                    |  |  |
| Diarrhea                             |                        |  |  |
| subjects affected / exposed          | 912 / 2864<br>(31.84%) |  |  |
| occurrences (all)                    | 1804                   |  |  |
| Constipation                         |                        |  |  |
| subjects affected / exposed          | 497 / 2864<br>(17.35%) |  |  |
| occurrences (all)                    | 600                    |  |  |
| Nausea                               |                        |  |  |
| subjects affected / exposed          | 483 / 2864<br>(16.86%) |  |  |
| occurrences (all)                    | 635                    |  |  |
| Dry mouth                            |                        |  |  |
| subjects affected / exposed          | 151 / 2864 (5.27%)     |  |  |
| occurrences (all)                    | 173                    |  |  |
| Mucositis oral                       |                        |  |  |
| subjects affected / exposed          | 780 / 2864<br>(27.23%) |  |  |
| occurrences (all)                    | 1164                   |  |  |
| Vomiting                             |                        |  |  |

|   |                         |  |  |
|---|-------------------------|--|--|
| subjects affected / exposed                     | 375 / 2864<br>(13.09%)  |  |  |
| occurrences (all)                               | 516                     |  |  |
| Skin and subcutaneous tissue disorders          |                         |  |  |
| Palmar-plantar erythrodysesthesia syndrome      |                         |  |  |
| subjects affected / exposed                     | 1220 / 2864<br>(42.60%) |  |  |
| occurrences (all)                               | 3167                    |  |  |
| Rash maculo-papular                             |                         |  |  |
| subjects affected / exposed                     | 310 / 2864<br>(10.82%)  |  |  |
| occurrences (all)                               | 445                     |  |  |
| Dry skin  |                         |  |  |
| subjects affected / exposed                     | 178 / 2864 (6.22%)      |  |  |
| occurrences (all)                               | 241                     |  |  |
| Rash acneiform                                  |                         |  |  |
| subjects affected / exposed                     | 180 / 2864 (6.28%)      |  |  |
| occurrences (all)                               | 252                     |  |  |
| Renal and urinary disorders                     |                         |  |  |
| Proteinuria                                     |                         |  |  |
| subjects affected / exposed                     | 268 / 2864 (9.36%)      |  |  |
| occurrences (all)                               | 443                     |  |  |
| Endocrine disorders                             |                         |  |  |
| Hypothyroidism                                  |                         |  |  |
| subjects affected / exposed                     | 177 / 2864 (6.18%)      |  |  |
| occurrences (all)                               | 212                     |  |  |
| Musculoskeletal and connective tissue disorders |                         |  |  |
| Myalgia   |                         |  |  |
| subjects affected / exposed                     | 181 / 2864 (6.32%)      |  |  |
| occurrences (all)                               | 225                     |  |  |
| Pain in extremity                               |                         |  |  |
| subjects affected / exposed                     | 191 / 2864 (6.67%)      |  |  |
| occurrences (all)                               | 259                     |  |  |
| Back pain                                       |                         |  |  |
| subjects affected / exposed                     | 273 / 2864 (9.53%)      |  |  |
| occurrences (all)                               | 376                     |  |  |
| Infections and infestations                     |                         |  |  |

|  |                                |  |  |
|--|--------------------------------|--|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                | 211 / 2864 (7.37%)<br>255      |  |  |
| Metabolism and nutrition disorders<br>Hypophosphatemia<br>subjects affected / exposed<br>occurrences (all) | 333 / 2864<br>(11.63%)<br>786  |  |  |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)   | 997 / 2864<br>(34.81%)<br>1407 |  |  |
| Hypokalemia<br>subjects affected / exposed<br>occurrences (all)  | 197 / 2864 (6.88%)<br>290      |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 03 August 2012    | <ol style="list-style-type: none"><li>1. Inclusion criteria concerning previous therapy for KRAS unknown subjects and acceptable limits for total bilirubin in subjects with documented Gilbert's Syndrome were made consistent with the preceding CORRECT trial to avoid uncertainty among the investigators.</li><li>2. Introduction of a more flexible and individualized schedule of liver function monitoring during treatment, where alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin must be monitored closely, at least every two weeks during the first 2 cycles of treatment.</li><li>3. Addition of a time window for coagulation measurements on Day 1 of Cycle 1.</li><li>4. Determination of a timeframe for blood and urine sample collection prior to dosing, during treatment phase.</li><li>5. Changes to make the text consistent with the eCRF concerning demographic and baseline characteristics, and with other study documents (Study Drug Reconciliation and Destruction Log, interactive voice response system (IVRS)/interactive web response system (IWRS) site manual).</li></ol> |
| 17 September 2012 | <ol style="list-style-type: none"><li>1. Modification in the wording of the inclusion criterion concerning KRAS negative or unknown subjects, allowing the inclusion of subjects who have not received prior therapy with bevacizumab and cetuximab / panitumumab.</li><li>2. Clarification about the planning of subgroup analyses for Mexican and Russian populations.</li></ol>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported