



## Clinical trial results: AG-013736 (Axitinib) for the Treatment of Metastatic Renal Cell Cancer Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-018585-23 |
| Trial protocol           | BG             |
| Global end of trial date | 29 April 2021  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 06 May 2022  |
| First version publication date | 06 May 2022  |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A4061051 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00920816 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Pfizer Inc.  |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017   |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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                       | 09 July 2021  |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 29 April 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

Compare the progression-free survival (PFS) of treatment-naïve subjects with metastatic renal cell carcinoma (mRCC) receiving AG-013736 versus sorafenib.

Estimate the PFS of previously-treated Asian subjects with mRCC receiving AG-013736 versus sorafenib.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 25 August 2009 |
| Long term follow-up planned                               | Yes            |
| Long term follow-up rationale                             | Safety         |
| Long term follow-up duration                              | 3 Years        |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                            |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 11 |
| Country: Number of subjects enrolled | Bulgaria: 2                |
| Country: Number of subjects enrolled | Chile: 29                  |
| Country: Number of subjects enrolled | India: 35                  |
| Country: Number of subjects enrolled | Malaysia: 6                |
| Country: Number of subjects enrolled | Mexico: 11                 |
| Country: Number of subjects enrolled | Philippines: 14            |
| Country: Number of subjects enrolled | Romania: 14                |
| Country: Number of subjects enrolled | Russian Federation: 58     |
| Country: Number of subjects enrolled | South Africa: 1            |
| Country: Number of subjects enrolled | Ukraine: 61                |
| Country: Number of subjects enrolled | United States: 29          |
| Country: Number of subjects enrolled | Taiwan: 6                  |
| Worldwide total number of subjects   | 277                        |
| EEA total number of subjects         | 16                         |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 213 |
| From 65 to 84 years                       | 63  |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

First-line subjects included all treatment-naïve subjects with metastatic renal cell cancer (mRCC) from global and second-line subjects included all previously-treated Asian subjects with mRCC.

### Pre-assignment

Screening details:

All China subjects were excluded from safety analysis due to inability to obtain timely approval to use data in accordance with Human Genetic Resources Administration of China (HGRAC) regulation.

### Period 1

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

### Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | Axitinib (First-line Subjects) |

Arm description:

Subjects (excluding subjects from China) with no prior systemic first-line therapy received axitinib (AG-013736) tablet at a starting dose of 5 milligram (mg) orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

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

Dosage and administration details:

5 mg

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Sorafenib (First-line Subjects) |
|------------------|---------------------------------|

Arm description:

Subjects (excluding subjects from China) with no prior systemic first-line therapy received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

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

Dosage and administration details:

400 mg

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Axitinib (Second-line Subjects) |
|------------------|---------------------------------|

Arm description:

Asian subjects (excluding subjects from China) with prior systemic first-line therapy containing sunitinib or cytokine received axitinib (AG-013736) tablet at a starting dose of 5 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Axitinib                         |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Tablet                           |
| Routes of administration               | Oral use                         |
| Dosage and administration details:     |                                  |
| 5 mg                                   |                                  |
| <b>Arm title</b>                       | Sorafenib (Second-line Subjects) |

Arm description:

Asian subjects (excluding subjects from China) with prior systemic first-line therapy containing sunitinib or cytokine received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

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

Dosage and administration details:

5 mg

| <b>Number of subjects in period 1</b> | Axitinib (First-line Subjects) | Sorafenib (First-line Subjects) | Axitinib (Second-line Subjects) |
|---------------------------------------|--------------------------------|---------------------------------|---------------------------------|
| Started                               | 173                            | 88                              | 11                              |
| Completed                             | 0                              | 0                               | 0                               |
| Not completed                         | 173                            | 88                              | 11                              |
| Global deterioration of health status | 2                              | -                               | -                               |
| Subject refused treatment             | 11                             | 5                               | 1                               |
| Adverse event                         | 1                              | 1                               | 1                               |
| Subject died                          | 116                            | 63                              | 8                               |
| Unspecified                           | 26                             | 15                              | 1                               |
| Lost to follow-up                     | 11                             | 2                               | -                               |
| Objective progression or relapse      | 6                              | 2                               | -                               |

| <b>Number of subjects in period 1</b> | Sorafenib (Second-line Subjects) |
|---------------------------------------|----------------------------------|
| Started                               | 5                                |
| Completed                             | 0                                |
| Not completed                         | 5                                |
| Global deterioration of health status | -                                |
| Subject refused treatment             | -                                |
| Adverse event                         | -                                |
| Subject died                          | 3                                |
| Unspecified                           | 2                                |
| Lost to follow-up                     | -                                |

|                                  |   |
|----------------------------------|---|
| Objective progression or relapse | - |
|----------------------------------|---|

## Baseline characteristics

### Reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | Axitinib (First-line Subjects)   |
| Reporting group description:   |                                  |
| Subjects (excluding subjects from China) with no prior systemic first-line therapy received axitinib (AG-013736) tablet at a starting dose of 5 milligram (mg) orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.                         |                                  |
| Reporting group title  | Sorafenib (First-line Subjects)  |
| Reporting group description:   |                                  |
| Subjects (excluding subjects from China) with no prior systemic first-line therapy received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.  |                                  |
| Reporting group title  | Axitinib (Second-line Subjects)  |
| Reporting group description:   |                                  |
| Asian subjects (excluding subjects from China) with prior systemic first-line therapy containing sunitinib or cytokine received axitinib (AG-013736) tablet at a starting dose of 5 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks. |                                  |
| Reporting group title  | Sorafenib (Second-line Subjects) |
| Reporting group description:   |                                  |
| Asian subjects (excluding subjects from China) with prior systemic first-line therapy containing sunitinib or cytokine received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.          |                                  |

| Reporting group values | Axitinib (First-line Subjects) | Sorafenib (First-line Subjects) | Axitinib (Second-line Subjects) |
|------------------------|--------------------------------|---------------------------------|---------------------------------|
| Number of subjects     | 173                            | 88                              | 11                              |
| Age Categorical        |                                |                                 |                                 |
| Units: Subjects        |                                |                                 |                                 |
| 18-64 years            | 126                            | 72                              | 10                              |
| >=65 years             | 47                             | 16                              | 1                               |
| Sex: Female, Male      |                                |                                 |                                 |
| Units: Subjects        |                                |                                 |                                 |
| Male                   | 122                            | 69                              | 8                               |
| Female                 | 51                             | 19                              | 3                               |

| Reporting group values | Sorafenib (Second-line Subjects) | Total |  |
|------------------------|----------------------------------|-------|--|
| Number of subjects     | 5                                | 277   |  |
| Age Categorical        |                                  |       |  |
| Units: Subjects        |                                  |       |  |
| 18-64 years            | 5                                | 213   |  |
| >=65 years             | 0                                | 64    |  |
| Sex: Female, Male      |                                  |       |  |
| Units: Subjects        |                                  |       |  |
| Male                   | 3                                | 202   |  |
| Female                 | 2                                | 75    |  |

## End points

### End points reporting groups

|  |                                       |
|--|---------------------------------------|
| Reporting group title  | Axitinib (First-line Subjects)        |
| Reporting group description:<br>Subjects (excluding subjects from China) with no prior systemic first-line therapy received axitinib (AG-013736) tablet at a starting dose of 5 milligram (mg) orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.                         |                                       |
| Reporting group title  | Sorafenib (First-line Subjects)       |
| Reporting group description:<br>Subjects (excluding subjects from China) with no prior systemic first-line therapy received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.  |                                       |
| Reporting group title  | Axitinib (Second-line Subjects)       |
| Reporting group description:<br>Asian subjects (excluding subjects from China) with prior systemic first-line therapy containing sunitinib or cytokine received axitinib (AG-013736) tablet at a starting dose of 5 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks. |                                       |
| Reporting group title  | Sorafenib (Second-line Subjects)      |
| Reporting group description:<br>Asian subjects (excluding subjects from China) with prior systemic first-line therapy containing sunitinib or cytokine received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.          |                                       |
| Subject analysis set title   | Axitinib (First-line Subjects): PCD   |
| Subject analysis set type  | Full analysis                         |
| Subject analysis set description:<br>All subjects with no prior systemic first-line therapy received axitinib (AG-013736) tablet at a starting dose of 5 milligram (mg) orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.  |                                       |
| Subject analysis set title   | Sorafenib (First-line Subjects): PCD  |
| Subject analysis set type  | Full analysis                         |
| Subject analysis set description:<br>All subjects with no prior systemic first-line therapy received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.   |                                       |
| Subject analysis set title   | Axitinib (Second-line Subjects): PCD  |
| Subject analysis set type  | Full analysis                         |
| Subject analysis set description:<br>All Asian subjects with prior systemic first-line therapy containing sunitinib or cytokine received axitinib (AG-013736) tablet at a starting dose of 5 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.                        |                                       |
| Subject analysis set title   | Sorafenib (Second-line Subjects): PCD |
| Subject analysis set type  | Full analysis                         |
| Subject analysis set description:<br>All Asian subjects with prior systemic first-line therapy containing sunitinib or cytokine received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.                                 |                                       |

### Primary: Progression Free Survival (PFS): First-Line Subjects

|  |  |
|--|--|
| End point title  | Progression Free Survival (PFS): First-Line Subjects |
| End point description:<br>Time in months from randomisation to first documentation of objective tumour progression or death due to any cause. PFS calculated as (first event date minus date of randomisation plus 1)/30.4. Tumour |  |



progression determined from oncologic assessment data (where it meets criteria for progressive disease [PD]), or from adverse event (AE) data (where outcome was "Death"). Progression using Response Evaluation Criteria in Solid Tumours (RECIST) is  $\geq 20$  percent (%) increase in sum of longest diameter of target lesions; measurable increase in non-target lesion; appearance of new lesions. Full analysis set (FAS) included all previously-treated Asian subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug, or received a different drug from that to which they were randomised.

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

End point timeframe:

Baseline until disease progression or death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 107)

| End point values                 | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|----------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type               | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed      | 192                                 | 96                                   |  |  |
| Units: months                    |                                     |                                      |  |  |
| median (confidence interval 95%) | 10.1 (7.2 to 12.1)                  | 6.5 (4.7 to 8.3)                     |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Axitinib vs Sorafenib: First line, PCD |
|----------------------------|--|

Statistical analysis description:

First-line subjects: hazard ratio was stratified by eastern cooperative oncology group (ECOG) performance status (0 versus 1).

|   |  |
|---|--|
| Comparison groups                       | Axitinib (First-line Subjects): PCD v Sorafenib (First-line Subjects): PCD |
| Number of subjects included in analysis | 288  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.767  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.559  |
| upper limit                             | 1.053  |

## Primary: Progression Free Survival (PFS): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Progression Free Survival (PFS): Second-Line Subjects |
|-----------------|---|

End point description:

Time in months from randomisation to first documentation of objective tumour progression or death due to any cause. PFS calculated as (first event date minus date of randomisation plus 1)/30.4. Tumour progression determined from oncologic assessment data (where it meets criteria for progressive disease [PD]), or from adverse event (AE) data (where outcome was "Death"). Progression using Response Evaluation Criteria in Solid Tumours (RECIST) is  $\geq 20\%$  increase in sum of longest diameter of target lesions; measurable increase in non-target lesion; appearance of new lesions. FAS included all

previously-treated Asian subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug, or received a different drug from that to which they were randomised.

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:  |         |
| Baseline until disease progression or death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 103) |         |

| End point values                 | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|----------------------------------|--|---|--|--|
| Subject group type               | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed      | 135  | 69  |  |  |
| Units: months                    |  |   |  |  |
| median (confidence interval 95%) | 6.5 (4.7 to 9.1)                           | 4.8 (3.0 to 6.5)                            |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Axitinib vs Sorafenib: Second line, PCD                                      |
| Statistical analysis description:  |  |
| Second-line subjects: hazard ratio was stratified by eastern cooperative oncology group (ECOG) performance status (0 versus 1) and prior treatment (sunitinib versus cytokine-containing regimen). |  |
| Comparison groups  | Axitinib (Second-line Subjects): PCD v Sorafenib (Second-line Subjects): PCD |
| Number of subjects included in analysis  | 204  |
| Analysis specification   | Pre-specified  |
| Analysis type  | superiority  |
| Parameter estimate   | Hazard ratio (HR)  |
| Point estimate   | 0.731  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.506  |
| upper limit  | 1.058  |

## Secondary: Percentage of Subjects With Objective Response (OR): First-Line Subjects

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Objective Response (OR): First-Line Subjects |
|-----------------|--|

End point description:

Percentage of subjects with OR based on assessment of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST. Confirmed response were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. CR was defined as disappearance of all lesions (target and/or non target). PR were those with at least 30% decrease in sum of the longest dimensions of target lesions taking as a reference the baseline sum longest dimensions, with non target lesions not increased or absent. FAS included all previously-treated Asian subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug, or received a different drug from that to which they were randomised.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Baseline until disease progression or death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 107) |           |

| End point values                 | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|----------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type               | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed      | 192                                 | 96                                   |  |  |
| Units: percentage of subjects    |                                     |                                      |  |  |
| number (confidence interval 95%) | 32.3 (25.7 to 39.4)                 | 14.6 (8.2 to 23.3)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Objective Response (OR): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Objective Response (OR): Second-Line Subjects |
|-----------------|---|

End point description:

Percentage of subjects with OR based on assessment of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST. Confirmed response were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. CR was defined as disappearance of all lesions (target and/or non target). PR were those with at least 30% decrease in sum of the longest dimensions of target lesions taking as a reference the baseline sum longest dimensions, with non target lesions not increased or absent. FAS included all previously-treated Asian subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug, or received a different drug from that to which they were randomised.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Baseline until disease progression or death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 103) |           |

| End point values                 | Axitinib (Second-line Subjects): PCD | Sorafenib (Second-line Subjects): PCD |  |  |
|----------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type               | Subject analysis set                 | Subject analysis set                  |  |  |
| Number of subjects analysed      | 135                                  | 69                                    |  |  |
| Units: percentage of subjects    |                                      |                                       |  |  |
| number (confidence interval 95%) | 23.7 (16.8 to 31.8)                  | 10.1 (4.2 to 19.8)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DR): First-Line Subjects

|                 |  |
|-----------------|--|
| End point title | Duration of Response (DR): First-Line Subjects |
|-----------------|--|

End point description:

Time in months from the first documentation of objective tumour response that is subsequently confirmed to objective tumour progression or death due to any cause. Duration of tumour response was calculated as (the date of the first documentation of objective tumour progression or death due to any cause minus the date of the first CR or PR that was subsequently confirmed plus 1) divided by 30.4. DR was calculated for the subgroup of subjects with a confirmed objective tumour response. DR was calculated for the subgroup of subjects from the FAS treatment-naïve population, with a confirmed objective tumour response (CR or PR). '99999' signifies that upper limit of CI was not estimable because subjects were still responding to medication as the study was ongoing at the time of primary completion analysis and this analysis was final.

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

End point timeframe:

Baseline until disease progression or death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 107)

| End point values                 | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|----------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type               | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed      | 62                                  | 14                                   |  |  |
| Units: months                    |                                     |                                      |  |  |
| median (confidence interval 95%) | 14.7 (11.0 to 99999)                | 14.3 (11.3 to 99999)                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DR): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Duration of Response (DR): Second-Line Subjects |
|-----------------|---|

End point description:

Time in months from the first documentation of objective tumour response that is subsequently confirmed to objective tumour progression or death due to any cause. Duration of tumour response was calculated as (the date of the first documentation of objective tumour progression or death due to any cause minus the date of the first CR or PR that was subsequently confirmed plus 1) divided by 30.4. DR was calculated for the subgroup of subjects with a confirmed objective tumour response. DR was calculated for the subgroup of subjects from the FAS previously-treated population, with a confirmed objective tumour response (CR or PR). '99999' signifies that median and upper limit of CI was not estimable because subjects were still responding to medication as the study was ongoing at the time of primary completion analysis and this analysis was final.

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

End point timeframe:

Baseline until disease progression or death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 103)

| End point values                 | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|----------------------------------|--|---|--|--|
| Subject group type               | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed      | 32   | 7   |  |  |
| Units: months                    |  |   |  |  |
| median (confidence interval 95%) | 99999 (12.5 to 99999)                      | 8.7 (4.1 to 99999)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS): First-Line Subjects

|  |  |
|--|--|
| End point title  | Overall Survival (OS): First-Line Subjects |
| End point description:   |  |
| Time in months from date of randomisation to date of death due to any cause. OS was calculated as (the death date minus the date of randomisation plus 1) divided by 30.4. Death was determined from adverse event data (where outcome was death) or from follow-up contact data (where the subject current status was death). FAS included all treatment-naïve subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug, or received a different drug from that to which they were randomised. "99999" signifies that median and upper limit of the CI was not reachable as data was not matured at the time of the analysis as the study was ongoing at the time of primary completion analysis and this analysis was final. |  |
| End point type   | Secondary                                  |
| End point timeframe:   |  |
| Baseline until death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 107)   |  |

| End point values                 | Axitinib (First-line<br>Subjects): PCD | Sorafenib<br>(First-line<br>Subjects): PCD |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Subject analysis set                   | Subject analysis set                       |  |  |
| Number of subjects analysed      | 192                                    | 96   |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 99999 (18.1 to 99999)                  | 99999 (18.1 to 99999)                      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Overall Survival (OS): Second-Line Subjects |
|-----------------|---|

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**End point description:**

Time in months from date of randomisation to date of death due to any cause. OS was calculated as (the death date minus the date of randomisation plus 1) divided by 30.4. Death was determined from adverse event data (where outcome was death) or from follow-up contact data (where the subject current status was death). FAS included all treatment-naïve subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug, or received a different drug from that to which they were randomised. "99999" signifies that upper limit of the CI was not reachable as data was not matured at the time of the analysis as the study was ongoing at the time of primary completion analysis and this analysis was final.

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

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**End point timeframe:**

Baseline until death (assessed on Week 6, Week 12 and thereafter every 8 weeks up to Week 103)

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| End point values                 | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|----------------------------------|--|---|--|--|
| Subject group type               | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed      | 135  | 69  |  |  |
| Units: months                    |  |   |  |  |
| median (confidence interval 95%) | 17.2 (14.8 to 99999)                       | 18.1 (12.1 to 99999)                        |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Other pre-specified: Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15): First-Line Subjects**

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|                 |  |
|-----------------|--|
| End point title | Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15): First-Line Subjects |
|-----------------|--|

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**End point description:**

FKSI-15 questionnaires (lack of energy, side effects, pain, weight loss, bone pain, fatigue, enjoying life, short of breath, worsened condition, appetite, coughing, bothered by fevers, ability to work, hematuria, sleep) was used to assess quality of life (QoL) for those diagnosed with renal cell cancer. Questions answered on 5-point Likert scale: 0 to 4 (0= not at all, 1= little bit, 2= somewhat, 3= quite a bit, 4= very much). Total FKSI score 0 to 60; higher scores=better health states (Individual questions may be reversed coded, as appropriate). FAS treatment-naïve population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively.

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|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

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**End point timeframe:**

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C23, end of treatment (up to Week 107), follow-up (28 days after last dose)

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| End point values                     | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|--------------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type                   | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed          | 183                                 | 95                                   |  |  |
| Units: units on a scale              |                                     |                                      |  |  |
| arithmetic mean (standard deviation) |                                     |                                      |  |  |
| C1 D1 (n= 183, 95)                   | 43.869 (± 8.117)                    | 43.865 (± 6.723)                     |  |  |
| C2 D1 (n= 176, 90)                   | 43.328 (± 7.630)                    | 43.969 (± 6.286)                     |  |  |
| C3 D1 (n= 164, 84)                   | 43.366 (± 7.192)                    | 43.345 (± 6.878)                     |  |  |
| C4 D1 (n= 156, 81)                   | 42.932 (± 7.566)                    | 42.926 (± 7.324)                     |  |  |
| C5 D1 (n= 153, 77)                   | 43.211 (± 7.578)                    | 44.022 (± 6.714)                     |  |  |
| C6 D1 (n= 141, 72)                   | 42.787 (± 8.098)                    | 42.344 (± 6.685)                     |  |  |
| C7 D1 (n= 139, 65)                   | 42.474 (± 7.926)                    | 43.446 (± 6.931)                     |  |  |
| C8 D1 (n= 131, 60)                   | 42.534 (± 7.510)                    | 44.077 (± 6.986)                     |  |  |
| C9 D1 (n= 126, 59)                   | 42.778 (± 8.229)                    | 44.051 (± 7.234)                     |  |  |
| C10 D1 (n= 122, 55)                  | 43.120 (± 7.966)                    | 44.018 (± 6.751)                     |  |  |
| C11 D1 (n= 114, 48)                  | 43.264 (± 7.837)                    | 45.000 (± 6.130)                     |  |  |
| C12 D1 (n= 105, 44)                  | 43.962 (± 7.243)                    | 45.318 (± 6.440)                     |  |  |
| C13 D1 (n= 99, 44)                   | 44.141 (± 7.289)                    | 45.787 (± 6.526)                     |  |  |
| C14 D1 (n= 95, 37)                   | 43.789 (± 7.985)                    | 45.459 (± 6.535)                     |  |  |
| C15 D1 (n= 85, 37)                   | 44.176 (± 8.055)                    | 45.514 (± 5.914)                     |  |  |
| C16 D1 (n= 82, 33)                   | 44.232 (± 7.515)                    | 46.000 (± 5.651)                     |  |  |
| C17 D1 (n= 78, 30)                   | 43.897 (± 8.456)                    | 46.400 (± 6.262)                     |  |  |
| C18 D1 (n= 71, 28)                   | 43.761 (± 8.019)                    | 45.357 (± 6.983)                     |  |  |
| C19 D1 (n= 57, 24)                   | 43.737 (± 7.413)                    | 45.583 (± 7.366)                     |  |  |
| C20 D1 (n= 45, 21)                   | 43.733 (± 7.605)                    | 44.333 (± 7.066)                     |  |  |
| C21 D1 (n= 36, 18)                   | 45.417 (± 6.240)                    | 43.500 (± 7.687)                     |  |  |
| C22 D1 (n= 23, 12)                   | 47.000 (± 5.985)                    | 45.833 (± 5.937)                     |  |  |
| C23 D1 (n= 14, 7)                    | 47.571 (± 6.357)                    | 45.714 (± 6.651)                     |  |  |
| End of treatment (n= 72, 42)         | 39.052 (± 9.109)                    | 39.524 (± 8.896)                     |  |  |
| Follow-up (n= 41, 26)                | 39.683 (± 11.132)                   | 40.038 (± 9.897)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15): Second-Line Subjects |
|-----------------|---|

End point description:

FKSI-15 questionnaires (lack of energy, side effects, pain, weight loss, bone pain, fatigue, enjoying life, short of breath, worsened condition, appetite, coughing, bothered by fevers, ability to work, hematuria, sleep) was used to assess quality of life (QoL) for those diagnosed with renal cell cancer. Questions answered on 5-point Likert scale: 0 to 4 (0= not at all, 1= little bit, 2= somewhat, 3= quite a bit, 4= very much). Total FKSI score 0 to 60; higher scores=better health states (Individual questions may be reversed coded, as appropriate). FAS previously-treated Asian population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C21, end of treatment (up to Week 103), follow-up (28 days after last dose)

| End point values                     | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed          | 134  | 69  |  |  |
| Units: units on a scale              |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| C1 D1 (n= 134, 69)                   | 46.753 (± 6.692)                           | 47.470 (± 7.450)                            |  |  |
| C2 D1 (n= 127, 66)                   | 46.217 (± 7.028)                           | 45.045 (± 7.478)                            |  |  |
| C3 D1 (n= 124, 57)                   | 45.968 (± 7.237)                           | 45.684 (± 7.756)                            |  |  |
| C4 D1 (n= 116, 53)                   | 45.060 (± 8.040)                           | 45.792 (± 7.762)                            |  |  |
| C5 D1 (n= 111, 48)                   | 45.775 (± 7.797)                           | 46.125 (± 7.491)                            |  |  |
| C6 D1 (n= 108, 41)                   | 45.407 (± 7.274)                           | 46.341 (± 7.213)                            |  |  |
| C7 D1 (n= 100, 38)                   | 45.709 (± 8.263)                           | 45.053 (± 7.843)                            |  |  |
| C8 D1 (n= 89, 37)                    | 45.169 (± 7.609)                           | 45.676 (± 9.357)                            |  |  |
| C9 D1 (n= 82, 33)                    | 45.829 (± 7.442)                           | 45.970 (± 8.487)                            |  |  |
| C10 D1 (n= 74, 27)                   | 45.608 (± 8.299)                           | 46.148 (± 8.156)                            |  |  |
| C11 D1 (n= 66, 22)                   | 45.833 (± 7.599)                           | 47.227 (± 6.611)                            |  |  |
| C12 D1 (n= 59, 22)                   | 45.797 (± 6.967)                           | 48.091 (± 6.414)                            |  |  |
| C13 D1 (n= 55, 20)                   | 46.727 (± 7.307)                           | 47.600 (± 5.762)                            |  |  |
| C14 D1 (n= 50, 15)                   | 47.740 (± 7.094)                           | 49.133 (± 5.235)                            |  |  |



|                              |                  |                   |  |  |
|------------------------------|------------------|-------------------|--|--|
| C15 D1 (n= 44, 13)           | 48.023 (± 6.297) | 49.308 (± 4.111)  |  |  |
| C16 D1 (n= 38, 12)           | 48.184 (± 6.186) | 50.500 (± 3.989)  |  |  |
| C17 D1 (n= 33, 10)           | 47.909 (± 6.866) | 49.000 (± 5.869)  |  |  |
| C18 D1 (n= 29, 8)            | 48.138 (± 6.791) | 49.125 (± 5.139)  |  |  |
| C19 D1 (n= 22, 7)            | 48.636 (± 5.206) | 48.571 (± 7.458)  |  |  |
| C20 D1 (n= 21, 6)            | 48.810 (± 6.478) | 50.500 (± 4.637)  |  |  |
| C21 D1 (n= 16, 6)            | 50.188 (± 5.588) | 50.000 (± 5.177)  |  |  |
| End of treatment (n= 37, 27) | 41.432 (± 9.188) | 42.889 (± 8.846)  |  |  |
| Follow-up (n= 13, 12)        | 35.385 (± 7.795) | 38.583 (± 11.556) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms (FKSI-DRS): First-Line Subjects

|                 |  |
|-----------------|--|
| End point title | Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms (FKSI-DRS): First-Line Subjects |
|-----------------|--|

End point description:

FKSI-DRS: subset of FKSI which is FACT-Kidney Symptom Index questionnaire used to assess QoL for subjects diagnosed with renal cell cancer. FKSI contains 15 questions and FKSI-DRS 9 questions (lack of energy, pain, losing weight, bone pain, fatigue, short of breath, coughing, bothered by fevers, hematuria) each ranging from 0 (not at all) to 4 (very much). FKSI-DRS total score 0 to 36; higher scores associated with better health states (Individual questions may be reversed coded, as appropriate). FAS treatment-naïve population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C23, end of treatment (up to Week 107), follow-up (28 days after last dose)

| End point values                     | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|--------------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type                   | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed          | 183                                 | 95                                   |  |  |
| Units: units on a scale              |                                     |                                      |  |  |
| arithmetic mean (standard deviation) |                                     |                                      |  |  |
| C1 D1 (n= 183, 95)                   | 28.691 (± 5.392)                    | 29.653 (± 4.699)                     |  |  |
| C2 D1 (n= 176, 90)                   | 28.728 (± 4.581)                    | 29.963 (± 3.817)                     |  |  |

|                              |                  |                  |  |  |
|------------------------------|------------------|------------------|--|--|
| C3 D1 (n= 164, 84)           | 29.171 (± 4.093) | 29.750 (± 4.095) |  |  |
| C4 D1 (n= 156, 81)           | 28.577 (± 4.305) | 29.642 (± 4.244) |  |  |
| C5 D1 (n= 153, 77)           | 29.020 (± 4.257) | 30.255 (± 3.668) |  |  |
| C6 D1 (n= 141, 72)           | 28.574 (± 4.674) | 29.153 (± 4.009) |  |  |
| C7 D1 (n= 139, 65)           | 28.568 (± 4.548) | 29.523 (± 4.051) |  |  |
| C8 D1 (n= 131, 60)           | 28.557 (± 4.308) | 30.296 (± 3.890) |  |  |
| C9 D1 (n= 126, 59)           | 28.817 (± 4.665) | 30.186 (± 4.392) |  |  |
| C10 D1 (n= 122, 55)          | 29.057 (± 4.484) | 30.364 (± 4.143) |  |  |
| C11 D1 (n= 114, 48)          | 29.146 (± 4.207) | 30.688 (± 3.926) |  |  |
| C12 D1 (n= 105, 44)          | 29.648 (± 3.752) | 30.727 (± 3.896) |  |  |
| C13 D1 (n= 99, 44)           | 29.545 (± 4.056) | 31.483 (± 3.602) |  |  |
| C14 D1 (n= 95, 37)           | 29.579 (± 4.186) | 31.027 (± 3.790) |  |  |
| C15 D1 (n= 85, 37)           | 29.859 (± 4.438) | 30.730 (± 3.724) |  |  |
| C16 D1 (n= 82, 33)           | 29.683 (± 4.242) | 31.515 (± 3.242) |  |  |
| C17 D1 (n= 78, 30)           | 29.564 (± 4.695) | 31.567 (± 3.884) |  |  |
| C18 D1 (n= 71, 28)           | 29.380 (± 4.752) | 31.107 (± 4.425) |  |  |
| C19 D1 (n= 57, 24)           | 29.737 (± 4.414) | 31.417 (± 3.911) |  |  |
| C20 D1 (n= 45, 21)           | 29.844 (± 4.527) | 30.762 (± 4.122) |  |  |
| C21 D1 (n= 36, 18)           | 30.889 (± 3.115) | 30.056 (± 4.372) |  |  |
| C22 D1 (n= 23, 12)           | 31.696 (± 3.081) | 31.000 (± 3.275) |  |  |
| C23 D1 (n= 14, 7)            | 31.357 (± 3.388) | 31.143 (± 4.413) |  |  |
| End of treatment (n= 72, 42) | 26.556 (± 5.487) | 26.786 (± 5.982) |  |  |
| Follow-up (n= 41, 26)        | 26.805 (± 6.373) | 26.769 (± 6.095) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms (FKSI-DRS): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms (FKSI-DRS): Second-Line Subjects |
|-----------------|---|

End point description:

FKSI-DRS: subset of FKSI which is FACT-Kidney Symptom Index questionnaire used to assess QoL for

subjects diagnosed with renal cell cancer. FKSI contains 15 questions and FKSI-DRS 9 questions (lack of energy, pain, losing weight, bone pain, fatigue, short of breath, coughing, bothered by fevers, hematuria) each ranging from 0 (not at all) to 4 (very much). FKSI-DRS total score 0 to 36; higher scores associated with better health states (Individual questions may be reversed coded, as appropriate). FAS previously-treated Asian population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C21, end of treatment (up to Week 103), follow-up (28 days after last dose)

| End point values                     | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed          | 134  | 69  |  |  |
| Units: units on a scale              |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| C1 D1 (n= 134, 69)                   | 31.020 (± 3.986)                           | 31.489 (± 4.538)                            |  |  |
| C2 D1 (n= 127, 66)                   | 30.600 (± 3.892)                           | 30.682 (± 3.895)                            |  |  |
| C3 D1 (n= 124, 57)                   | 30.645 (± 3.681)                           | 30.965 (± 3.803)                            |  |  |
| C4 D1 (n= 116, 53)                   | 30.103 (± 4.558)                           | 30.679 (± 3.980)                            |  |  |
| C5 D1 (n= 111, 48)                   | 30.676 (± 4.271)                           | 31.063 (± 3.629)                            |  |  |
| C6 D1 (n= 108, 41)                   | 30.731 (± 3.973)                           | 31.439 (± 4.249)                            |  |  |
| C7 D1 (n= 100, 38)                   | 30.920 (± 4.373)                           | 30.632 (± 4.365)                            |  |  |
| C8 D1 (n= 89, 37)                    | 30.966 (± 4.144)                           | 30.703 (± 5.195)                            |  |  |
| C9 D1 (n= 82, 33)                    | 31.012 (± 3.783)                           | 30.667 (± 4.884)                            |  |  |
| C10 D1 (n= 74, 27)                   | 30.986 (± 4.133)                           | 30.926 (± 4.215)                            |  |  |
| C11 D1 (n= 66, 22)                   | 31.212 (± 4.033)                           | 32.045 (± 3.579)                            |  |  |
| C12 D1 (n= 59, 22)                   | 31.356 (± 3.443)                           | 32.000 (± 3.338)                            |  |  |
| C13 D1 (n= 55, 20)                   | 31.418 (± 3.775)                           | 32.100 (± 2.989)                            |  |  |
| C14 D1 (n= 50, 15)                   | 32.100 (± 3.321)                           | 32.800 (± 2.274)                            |  |  |
| C15 D1 (n= 44, 13)                   | 32.000 (± 2.861)                           | 32.769 (± 2.279)                            |  |  |
| C16 D1 (n= 38, 12)                   | 31.921 (± 3.372)                           | 33.167 (± 2.167)                            |  |  |
| C17 D1 (n= 33, 10)                   | 32.061 (± 3.344)                           | 32.800 (± 2.898)                            |  |  |
| C18 D1 (n= 29, 8)                    | 31.931 (± 3.116)                           | 32.625 (± 2.615)                            |  |  |
| C19 D1 (n= 22, 7)                    | 32.364 (± 2.341)                           | 32.429 (± 4.429)                            |  |  |

|                              |                  |                  |  |  |
|------------------------------|------------------|------------------|--|--|
| C20 D1 (n= 21, 6)            | 31.905 (± 2.998) | 33.500 (± 2.168) |  |  |
| C21 D1 (n= 16, 6)            | 33.125 (± 2.473) | 33.500 (± 2.345) |  |  |
| End of treatment (n= 37, 27) | 28.216 (± 5.662) | 29.519 (± 4.661) |  |  |
| Follow-up (n= 13, 12)        | 24.692 (± 4.366) | 27.500 (± 6.762) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D) Index Score: First-Line Subjects

|                 |  |
|-----------------|--|
| End point title | Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D)<br>Index Score: First-Line Subjects |
|-----------------|--|

End point description:

EQ-5D: Subject rated questionnaire to assess health-related quality of life in terms of a single utility score. Health State Profile component assesses level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression; 1 indicates better health state (no problems); 3 indicates worst health state ("confined to bed"). Scoring formula developed by EuroQol Group assigns a utility value for each domain in the profile. Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state. FAS treatment-naïve population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C23, end of treatment (up to Week 107), follow-up (28 days after last dose)

| End point values                     | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|--------------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type                   | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed          | 183                                 | 94                                   |  |  |
| Units: units on a scale              |                                     |                                      |  |  |
| arithmetic mean (standard deviation) |                                     |                                      |  |  |
| C1 D1 (n= 183, 94)                   | 0.710 (± 0.254)                     | 0.712 (± 0.272)                      |  |  |
| C2 D1 (n= 175, 90)                   | 0.709 (± 0.214)                     | 0.693 (± 0.237)                      |  |  |
| C3 D1 (n= 163, 84)                   | 0.694 (± 0.251)                     | 0.687 (± 0.261)                      |  |  |
| C4 D1 (n= 156, 81)                   | 0.696 (± 0.235)                     | 0.668 (± 0.265)                      |  |  |
| C5 D1 (n= 153, 77)                   | 0.708 (± 0.221)                     | 0.673 (± 0.269)                      |  |  |
| C6 D1 (n= 140, 72)                   | 0.683 (± 0.263)                     | 0.641 (± 0.281)                      |  |  |
| C7 D1 (n= 139, 65)                   | 0.685 (± 0.225)                     | 0.676 (± 0.676)                      |  |  |

|                              |                 |                 |  |  |
|------------------------------|-----------------|-----------------|--|--|
| C8 D1 (n= 131, 60)           | 0.678 (± 0.274) | 0.717 (± 0.244) |  |  |
| C9 D1 (n= 126, 59)           | 0.704 (± 0.239) | 0.729 (± 0.202) |  |  |
| C10 D1 (n= 122, 55)          | 0.682 (± 0.277) | 0.723 (± 0.238) |  |  |
| C11 D1 (n= 114, 48)          | 0.698 (± 0.260) | 0.748 (± 0.199) |  |  |
| C12 D1 (n= 105, 44)          | 0.708 (± 0.227) | 0.742 (± 0.218) |  |  |
| C13 D1 (n= 99, 44)           | 0.708 (± 0.253) | 0.761 (± 0.220) |  |  |
| C14 D1 (n= 95, 37)           | 0.703 (± 0.260) | 0.731 (± 0.254) |  |  |
| C15 D1 (n= 85, 37)           | 0.689 (± 0.269) | 0.755 (± 0.225) |  |  |
| C16 D1 (n= 82, 33)           | 0.702 (± 0.244) | 0.775 (± 0.186) |  |  |
| C17 D1 (n= 78, 30)           | 0.706 (± 0.250) | 0.738 (± 0.250) |  |  |
| C18 D1 (n= 71, 28)           | 0.699 (± 0.259) | 0.777 (± 0.191) |  |  |
| C19 D1 (n= 56, 24)           | 0.713 (± 0.256) | 0.762 (± 0.261) |  |  |
| C20 D1 (n= 45, 21)           | 0.699 (± 0.261) | 0.710 (± 0.300) |  |  |
| C21 D1 (n= 36, 18)           | 0.712 (± 0.232) | 0.702 (± 0.307) |  |  |
| C22 D1 (n= 23, 12)           | 0.737 (± 0.255) | 0.774 (± 0.177) |  |  |
| C23 D1 (n= 14, 7)            | 0.736 (± 0.275) | 0.789 (± 0.187) |  |  |
| End of treatment (n= 70, 42) | 0.635 (± 0.268) | 0.588 (± 0.291) |  |  |
| Follow-up (n= 41, 26)        | 0.545 (± 0.434) | 0.618 (± 0.254) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D) Index Score: Second-Line Subjects

|                 |  |
|-----------------|--|
| End point title | Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D) Index Score: Second-Line Subjects |
|-----------------|--|

End point description:

EQ-5D: Subject rated questionnaire to assess health-related quality of life in terms of a single utility score. Health State Profile component assesses level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression; 1 indicates better health state (no problems); 3 indicates worst health state ("confined to bed"). Scoring formula developed by EuroQol Group assigns a utility value for each domain in the profile. Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state. FAS previously-treated Asian population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C21, end of treatment (up to Week

| End point values                     | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed          | 134  | 69  |  |  |
| Units: units on a scale              |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| C1 D1 (n= 134, 69)                   | 0.812 (±<br>0.225)                         | 0.831 (±<br>0.186)                          |  |  |
| C2 D1 (n= 127, 65)                   | 0.769 (±<br>0.218)                         | 0.754 (±<br>0.251)                          |  |  |
| C3 D1 (n= 124, 58)                   | 0.772 (±<br>0.206)                         | 0.755 (±<br>0.278)                          |  |  |
| C4 D1 (n= 116, 53)                   | 0.737 (±<br>0.272)                         | 0.759 (±<br>0.211)                          |  |  |
| C5 D1 (n= 111, 48)                   | 0.780 (±<br>0.203)                         | 0.768 (±<br>0.275)                          |  |  |
| C6 D1 (n= 108, 41)                   | 0.767 (±<br>0.251)                         | 0.753 (±<br>0.245)                          |  |  |
| C7 D1 (n= 100, 38)                   | 0.762 (±<br>0.252)                         | 0.768 (±<br>0.239)                          |  |  |
| C8 D1 (n= 89, 37)                    | 0.758 (±<br>0.241)                         | 0.733 (±<br>0.339)                          |  |  |
| C9 D1 (n= 82, 33)                    | 0.796 (±<br>0.203)                         | 0.794 (±<br>0.262)                          |  |  |
| C10 D1 (n= 74, 27)                   | 0.768 (±<br>0.243)                         | 0.820 (±<br>0.169)                          |  |  |
| C11 D1 (n= 66, 22)                   | 0.792 (±<br>0.210)                         | 0.848 (±<br>0.158)                          |  |  |
| C12 D1 (n= 59, 22)                   | 0.797 (±<br>0.201)                         | 0.837 (±<br>0.157)                          |  |  |
| C13 D1 (n= 55, 20)                   | 0.786 (±<br>0.217)                         | 0.814 (±<br>0.156)                          |  |  |
| C14 D1 (n= 50, 15)                   | 0.833 (±<br>0.162)                         | 0.871 (±<br>0.131)                          |  |  |
| C15 D1 (n= 44, 13)                   | 0.819 (±<br>0.151)                         | 0.829 (±<br>0.152)                          |  |  |
| C16 D1 (n= 38, 12)                   | 0.811 (±<br>0.186)                         | 0.828 (±<br>0.142)                          |  |  |
| C17 D1 (n= 33, 10)                   | 0.834 (±<br>0.158)                         | 0.865 (±<br>0.122)                          |  |  |
| C18 D1 (n= 29, 8)                    | 0.830 (±<br>0.164)                         | 0.829 (±<br>0.160)                          |  |  |
| C19 D1 (n= 22, 7)                    | 0.830 (±<br>0.148)                         | 0.861 (±<br>0.139)                          |  |  |
| C20 D1 (n= 21, 6)                    | 0.832 (±<br>0.163)                         | 0.923 (±<br>0.129)                          |  |  |
| C21 D1 (n= 16, 6)                    | 0.859 (±<br>0.155)                         | 0.852 (±<br>0.176)                          |  |  |
| End of treatment (n= 37, 27)         | 0.582 (±<br>0.406)                         | 0.623 (±<br>0.296)                          |  |  |
| Follow-up (n= 13, 12)                | 0.429 (±<br>0.358)                         | 0.418 (±<br>0.565)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D) Visual Analog Scale (VAS): First-Line Subjects

|  |   |
|--|---|
| End point title  | Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D) Visual Analog Scale (VAS): First-Line Subjects |
| End point description:   |   |
| EQ-5D: Subject rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0: worst imaginable health state to 100: best imaginable health state; higher scores indicate a better health state. FAS treatment-naïve population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those subjects evaluated for this endpoint at specific time points for each group respectively. |   |
| End point type   | Other pre-specified   |
| End point timeframe:   |   |
| Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C23, end of treatment (up to Week 107), follow-up (28 days after last dose)   |   |

| End point values                     | Axitinib (First-line Subjects): PCD | Sorafenib (First-line Subjects): PCD |  |  |
|--------------------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type                   | Subject analysis set                | Subject analysis set                 |  |  |
| Number of subjects analysed          | 182                                 | 94                                   |  |  |
| Units: units on a scale              |                                     |                                      |  |  |
| arithmetic mean (standard deviation) |                                     |                                      |  |  |
| C1 D1 (n= 182, 94)                   | 71.181 (± 19.641)                   | 72.362 (± 16.466)                    |  |  |
| C2 D1 (n= 175, 90)                   | 71.714 (± 16.583)                   | 72.422 (± 14.576)                    |  |  |
| C3 D1 (n= 165, 83)                   | 72.006 (± 16.971)                   | 71.241 (± 16.252)                    |  |  |
| C4 D1 (n= 156, 81)                   | 72.179 (± 16.980)                   | 72.086 (± 14.904)                    |  |  |
| C5 D1 (n= 153, 78)                   | 72.451 (± 18.237)                   | 73.615 (± 14.665)                    |  |  |
| C6 D1 (n= 141, 72)                   | 71.574 (± 18.929)                   | 69.944 (± 17.535)                    |  |  |
| C7 D1 (n= 139, 65)                   | 71.050 (± 18.967)                   | 73.923 (± 13.998)                    |  |  |
| C8 D1 (n= 131, 60)                   | 71.031 (± 19.081)                   | 73.183 (± 16.674)                    |  |  |
| C9 D1 (n= 126, 59)                   | 72.690 (± 18.789)                   | 73.780 (± 16.180)                    |  |  |
| C10 D1 (n= 122, 55)                  | 72.910 (± 19.354)                   | 72.400 (± 18.814)                    |  |  |
| C11 D1 (n= 114, 48)                  | 72.763 (± 18.174)                   | 72.271 (± 18.512)                    |  |  |

|                              |                   |                   |  |  |
|------------------------------|-------------------|-------------------|--|--|
| C12 D1 (n= 105, 44)          | 73.610 (± 18.275) | 75.295 (± 17.052) |  |  |
| C13 D1 (n= 99, 44)           | 73.030 (± 18.348) | 75.432 (± 17.907) |  |  |
| C14 D1 (n= 95, 37)           | 73.147 (± 17.546) | 75.108 (± 18.371) |  |  |
| C15 D1 (n= 85, 37)           | 74.494 (± 17.938) | 74.405 (± 17.650) |  |  |
| C16 D1 (n= 82, 33)           | 73.878 (± 18.289) | 75.818 (± 17.716) |  |  |
| C17 D1 (n= 78, 30)           | 73.090 (± 17.717) | 74.333 (± 18.654) |  |  |
| C18 D1 (n= 71, 28)           | 73.817 (± 17.288) | 75.571 (± 18.550) |  |  |
| C19 D1 (n= 56, 24)           | 72.089 (± 18.169) | 75.125 (± 20.919) |  |  |
| C20 D1 (n= 45, 21)           | 74.244 (± 17.044) | 74.190 (± 20.425) |  |  |
| C21 D1 (n= 36, 18)           | 75.694 (± 11.918) | 70.500 (± 21.637) |  |  |
| C22 D1 (n= 23, 12)           | 78.000 (± 12.544) | 73.917 (± 15.900) |  |  |
| C23 D1 (n= 14, 7)            | 77.143 (± 12.697) | 72.571 (± 14.820) |  |  |
| End of treatment (n= 71, 42) | 67.254 (± 19.495) | 67.048 (± 22.570) |  |  |
| Follow-up (n= 41, 26)        | 69.195 (± 20.366) | 64.885 (± 19.916) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D) Visual Analog Scale (VAS): Second-Line Subjects

|                 |   |
|-----------------|---|
| End point title | Euro Quality of Life Questionnaire- 5 Dimensions (EQ-5D)<br>Visual Analog Scale (VAS): Second-Line Subjects |
|-----------------|---|

End point description:

EQ-5D: Subject rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0: worst imaginable health state to 100: best imaginable health state; higher scores indicate a better health state. FAS previously-treated Asian population. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint and 'n' signifies those endpoint evaluated for this measure at specific time points for each group respectively.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Pre-dose on Cycle [C]1 Day [D]1), D1 of each cycle until C21, end of treatment (up to Week 103), follow-up (28 days after last dose)



| End point values                     | Axitinib<br>(Second-line<br>Subjects): PCD | Sorafenib<br>(Second-line<br>Subjects): PCD |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Subject analysis set                       | Subject analysis set                        |  |  |
| Number of subjects analysed          | 134  | 69  |  |  |
| Units: units on a scale              |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| C1 D1 (n= 134, 69)                   | 82.799 (±<br>13.351)                       | 82.058 (±<br>14.021)                        |  |  |
| C2 D1 (n= 127, 65)                   | 81.102 (±<br>13.895)                       | 78.231 (±<br>15.823)                        |  |  |
| C3 D1 (n= 124, 58)                   | 80.895 (±<br>13.387)                       | 80.534 (±<br>16.453)                        |  |  |
| C4 D1 (n= 116, 53)                   | 81.138 (±<br>13.508)                       | 81.245 (±<br>14.590)                        |  |  |
| C5 D1 (n= 111, 48)                   | 83.018 (±<br>12.829)                       | 80.250 (±<br>15.495)                        |  |  |
| C6 D1 (n= 108, 41)                   | 82.222 (±<br>13.793)                       | 80.829 (±<br>15.091)                        |  |  |
| C7 D1 (n= 100, 38)                   | 82.900 (±<br>13.287)                       | 80.868 (±<br>16.140)                        |  |  |
| C8 D1 (n= 89, 37)                    | 83.382 (±<br>12.636)                       | 81.000 (±<br>14.606)                        |  |  |
| C9 D1 (n= 82, 33)                    | 84.171 (±<br>11.260)                       | 83.788 (±<br>10.349)                        |  |  |
| C10 D1 (n= 74, 27)                   | 83.041 (±<br>13.042)                       | 82.778 (±<br>11.440)                        |  |  |
| C11 D1 (n= 66, 22)                   | 84.136 (±<br>14.231)                       | 83.000 (±<br>11.832)                        |  |  |
| C12 D1 (n= 59, 22)                   | 84.305 (±<br>13.211)                       | 83.500 (±<br>12.188)                        |  |  |
| C13 D1 (n= 55, 20)                   | 82.927 (±<br>17.317)                       | 83.300 (±<br>11.263)                        |  |  |
| C14 D1 (n= 50, 15)                   | 86.520 (±<br>10.831)                       | 86.667 (±<br>8.715)                         |  |  |
| C15 D1 (n= 44, 13)                   | 85.841 (±<br>11.783)                       | 86.462 (±<br>8.678)                         |  |  |
| C16 D1 (n= 38, 12)                   | 87.579 (±<br>10.391)                       | 86.083 (±<br>8.816)                         |  |  |
| C17 D1 (n= 33, 10)                   | 88.424 (±<br>10.866)                       | 84.300 (±<br>10.328)                        |  |  |
| C18 D1 (n= 29, 8)                    | 86.586 (±<br>13.605)                       | 83.125 (±<br>8.839)                         |  |  |
| C19 D1 (n= 22, 7)                    | 89.500 (±<br>8.684)                        | 82.143 (±<br>11.495)                        |  |  |
| C20 D1 (n= 21, 6)                    | 90.333 (±<br>8.679)                        | 86.000 (±<br>9.695)                         |  |  |
| C21 D1 (n= 16, 6)                    | 90.313 (±<br>9.741)                        | 84.167 (±<br>9.704)                         |  |  |
| End of treatment (n= 37, 27)         | 75.568 (±<br>17.934)                       | 74.741 (±<br>17.623)                        |  |  |
| Follow-up (n= 13, 12)                | 58.154 (±<br>20.760)                       | 64.333 (±<br>25.564)                        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to at least 3 years after the randomization of the last subject

Adverse event reporting additional description:

Same event may appear as both adverse event(AE) and serious AE(SAE). What is presented are distinct events. An event may be categorised as serious in 1 subject and as non-serious in another, or a subject may have experienced both serious and non-serious event. Safety analysis set. Safety reported for all subjects excluding subjects from China.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Axitinib (Second-line Subjects) |
|-----------------------|---------------------------------|

Reporting group description:

Asian subjects with prior systemic first-line therapy containing sunitinib or cytokine received axitinib (AG-013736) tablet at a starting dose of 5 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Sorafenib (Second-line Subjects) |
|-----------------------|----------------------------------|

Reporting group description:

Asian subjects with prior systemic first-line therapy containing sunitinib or cytokine received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Axitinib (First-line Subjects) |
|-----------------------|--------------------------------|

Reporting group description:

Subjects with no prior systemic first-line therapy received axitinib (AG-013736) tablet at a starting dose of 5 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Sorafenib (First-line Subjects) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects with no prior systemic first-line therapy received sorafenib tablet at a starting dose of 400 mg orally twice daily, dose adjustment was done based on the tolerability, as per investigator's discretion. Study medication was administered in cycles of 4 weeks.

| Serious adverse events  | Axitinib (Second-line Subjects) | Sorafenib (Second-line Subjects) | Axitinib (First-line Subjects) |
|---|---------------------------------|----------------------------------|--------------------------------|
| Total subjects affected by serious adverse events                   |                                 |                                  |                                |
| subjects affected / exposed   | 6 / 11 (54.55%)                 | 3 / 5 (60.00%)                   | 77 / 173 (44.51%)              |
| number of deaths (all causes)                                       | 9                               | 3                                | 117                            |
| number of deaths resulting from adverse events                      |                                 |                                  |                                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |                                  |                                |
| Cardiac neoplasm unspecified  |                                 |                                  |                                |
| subjects affected / exposed   | 0 / 11 (0.00%)                  | 0 / 5 (0.00%)                    | 1 / 173 (0.58%)                |
| occurrences causally related to treatment / all                     | 0 / 0                           | 0 / 0                            | 0 / 1                          |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                            | 0 / 0                          |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| Renal cancer                                    |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Renal cancer metastatic                         |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Renal cell carcinoma                            |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Tumour haemorrhage                              |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Malignant neoplasm progression                  |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 3 / 173 (1.73%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Lung neoplasm malignant                         |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Vascular disorders                              |                |               |                 |
| Angiopathy                                      |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Hypertensive crisis                             |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| General disorders and administration            |                |               |                 |

|   |                |                |                   |
|---|----------------|----------------|-------------------|
| site conditions                                 |                |                |                   |
| Death   |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0             |
| Multiple organ dysfunction syndrome             |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0             |
| Disease progression                             |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 20 / 173 (11.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 20            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 20            |
| Asthenia  |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 2 / 173 (1.16%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0             |
| Chest pain                                      |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 2 / 173 (1.16%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0             |
| General physical health deterioration           |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1             |
| Impaired healing                                |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0             |
| Mucosal inflammation                            |                |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1             |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0             |
| Pyrexia   |                |                |                   |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Sudden death                                    |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                |               |                 |
| Cough   |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Chronic obstructive pulmonary disease           |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Epistaxis                                       |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pleural effusion                                |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Pulmonary embolism                              |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Atelectasis                                     |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Dyspnoea  |                |               |                 |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Haemoptysis                                     |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pleurisy  |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pulmonary oedema                                |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Respiratory distress                            |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Respiratory failure                             |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Investigations                                  |                |               |                 |
| Haemoglobin decreased                           |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Injury, poisoning and procedural complications  |                |               |                 |
| Ankle fracture                                  |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| Facial bones fracture                           |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Humerus fracture                                |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Multiple injuries                               |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Patella fracture                                |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Upper limb fracture                             |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Wound dehiscence                                |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Hip fracture                                    |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Contusion                                       |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Cardiac disorders                               |                |               |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Angina pectoris                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Myocardial infarction                           |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 3 / 173 (1.73%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Myocardial ischaemia                            |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Acute myocardial infarction                     |                |                |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1           |
| Atrial flutter                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac arrest                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 3 / 173 (1.73%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 3           |
| Cardio-respiratory arrest                       |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 5 (20.00%) | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1           |
| Atrioventricular block second degree            |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ischaemic cardiomyopathy                        |                |                |                 |



|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                |                |                 |
| Axonal and demyelinating polyneuropathy         |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 5 (20.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Haemorrhagic stroke                             |                |                |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0           |
| Cerebrovascular accident                        |                |                |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0           |
| Ischaemic stroke                                |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cerebral haemorrhage                            |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Cerebral ischaemia                              |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Paraparesis                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Spinal cord compression                         |                |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Syncope   |                 |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                |                 |
| Anaemia   |                 |                |                 |
| subjects affected / exposed                     | 3 / 11 (27.27%) | 1 / 5 (20.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Thrombocytopenia                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                 |                |                 |
| Abdominal pain                                  |                 |                |                 |
| subjects affected / exposed                     | 2 / 11 (18.18%) | 1 / 5 (20.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Anal fistula                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Diarrhoea                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 8 / 173 (4.62%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 6 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastritis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Oesophagitis                                    |                 |                |                 |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Abdominal distension                            |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Gastric haemorrhage                             |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Gastric ulcer                                   |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Gastrointestinal haemorrhage                    |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 1 / 1           |
| Impaired gastric emptying                       |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1           |
| Melaena   |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Nausea  |                |               |                 |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Oesophageal varices haemorrhage                 |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Peptic ulcer                                    |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Proctitis                                       |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Rectal haemorrhage                              |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 3 / 173 (1.73%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Retroperitoneal haematoma                       |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Vomiting  |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Abdominal pain upper                            |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Aortoenteric fistula                            |                |               |                 |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 1 / 1           |
| Hepatobiliary disorders                         |                |               |                 |
| Cholecystitis                                   |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Cholecystitis acute                             |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                |               |                 |
| Erythema multiforme                             |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Palmar-plantar erythrodysaesthesia syndrome     |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Renal and urinary disorders                     |                |               |                 |
| Ureteric obstruction                            |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Dysuria   |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Haematuria                                      |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| Urinary retention                               |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |               |                 |
| Back pain                                       |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Muscular weakness                               |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pathological fracture                           |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Infections and infestations                     |                |               |                 |
| Cellulitis                                      |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Gastroenteritis                                 |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Upper respiratory tract infection               |                |               |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 5 (0.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Abscess   |                |               |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%) | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Cholecystitis infective                         |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 1 / 5 (20.00%) | 4 / 173 (2.31%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Pyelonephritis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sepsis  |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Skin bacterial infection                        |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Tonsillitis                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 2 / 173 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Wound infection                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Anal abscess                                    |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 5 (20.00%) | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                |                |                 |
| Decreased appetite                              |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dehydration                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 1 / 173 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hyperkalaemia                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

| <b>Serious adverse events</b>                                       | Sorafenib (First-line Subjects) |  |  |
|---|---------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                 |  |  |
| subjects affected / exposed   | 26 / 88 (29.55%)                |  |  |
| number of deaths (all causes)                                       | 63                              |  |  |
| number of deaths resulting from adverse events                      |                                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |  |  |
| Cardiac neoplasm unspecified  |                                 |  |  |
| subjects affected / exposed   | 0 / 88 (0.00%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Renal cancer  |                                 |  |  |
| subjects affected / exposed   | 0 / 88 (0.00%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Renal cancer metastatic   |                                 |  |  |



|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Renal cell carcinoma                                 |                |  |  |
| subjects affected / exposed                          | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 1          |  |  |
| Tumour haemorrhage                                   |                |  |  |
| subjects affected / exposed                          | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Malignant neoplasm progression                       |                |  |  |
| subjects affected / exposed                          | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Lung neoplasm malignant                              |                |  |  |
| subjects affected / exposed                          | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| Angiopathy   |                |  |  |
| subjects affected / exposed                          | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hypertensive crisis                                  |                |  |  |
| subjects affected / exposed                          | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Death  |                |  |  |
| subjects affected / exposed                          | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Multiple organ dysfunction syndrome             |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Disease progression                             |                |  |  |  |
| subjects affected / exposed                     | 6 / 88 (6.82%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 6          |  |  |  |
| deaths causally related to treatment / all      | 0 / 6          |  |  |  |
| Asthenia  |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Chest pain                                      |                |  |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| General physical health deterioration           |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Impaired healing                                |                |  |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Mucosal inflammation                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pyrexia   |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sudden death                                    |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Cough   |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Chronic obstructive pulmonary disease           |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Epistaxis                                       |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 3 / 88 (3.41%) |  |  |
| occurrences causally related to treatment / all | 1 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atelectasis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haemoptysis                                     |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleurisy  |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary oedema                                |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory distress                            |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory failure                             |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Haemoglobin decreased                           |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Ankle fracture                                  |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Facial bones fracture                           |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Humerus fracture                                |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Multiple injuries                               |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Patella fracture                                |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper limb fracture                             |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Wound dehiscence                                |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hip fracture                                    |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Contusion                                       |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Angina pectoris                                 |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Myocardial infarction                           |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Myocardial ischaemia                            |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Acute myocardial infarction                     |                |  |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atrial flutter                                  |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac arrest                                  |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardio-respiratory arrest                       |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atrioventricular block second degree            |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ischaemic cardiomyopathy                        |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Axonal and demyelinating polyneuropathy         |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Haemorrhagic stroke                             |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cerebrovascular accident                        |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Ischaemic stroke                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cerebral haemorrhage                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cerebral ischaemia                              |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Paraparesis                                     |                |  |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Spinal cord compression                         |                |  |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Syncope   |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Anaemia   |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thrombocytopenia                                |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 3 / 88 (3.41%) |  |  |
| occurrences causally related to treatment / all | 1 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anal fistula                                    |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences causally related to treatment / all | 1 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastritis                                       |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oesophagitis                                    |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper gastrointestinal haemorrhage              |                |  |  |



|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Abdominal distension                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastric haemorrhage                             |                |  |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastric ulcer                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Impaired gastric emptying                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Melaena   |                |  |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Nausea  |                |  |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Oesophageal varices haemorrhage                 |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Peptic ulcer                                    |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Proctitis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Rectal haemorrhage                              |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Retroperitoneal haematoma                       |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain upper                            |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Aortoenteric fistula                            |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholecystitis                                   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystitis acute                             |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Erythema multiforme                             |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Palmar-plantar erythrodysaesthesia syndrome     |                |  |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Ureteric obstruction                            |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dysuria   |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haematuria                                      |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary retention                               |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Musculoskeletal and connective tissue disorders |                |  |  |
| Back pain                                       |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Muscular weakness                               |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pathological fracture                           |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Cellulitis                                      |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abscess   |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystitis infective                         |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyelonephritis                                  |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sepsis  |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin bacterial infection                        |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tonsillitis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Wound infection                                 |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anal abscess                                    |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Decreased appetite<br>subjects affected / exposed  | 0 / 88 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          |  |  |
| Dehydration<br>subjects affected / exposed         | 1 / 88 (1.14%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 1          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          |  |  |
| Hyperkalaemia<br>subjects affected / exposed       | 2 / 88 (2.27%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 2          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>  | <b>Axitinib (Second-line<br/>Subjects)</b> | <b>Sorafenib (Second-<br/>line Subjects)</b> | <b>Axitinib (First-line<br/>Subjects)</b> |
|--|--|--|---|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                                | 11 / 11 (100.00%)                          | 5 / 5 (100.00%)                              | 161 / 173 (93.06%)                        |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Anal neoplasm<br>subjects affected / exposed | 0 / 11 (0.00%)                             | 1 / 5 (20.00%)                               | 0 / 173 (0.00%)                           |
| occurrences (all)  | 0  | 1  | 0   |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed  | 4 / 11 (36.36%)                            | 1 / 5 (20.00%)                               | 83 / 173 (47.98%)                         |
| occurrences (all)  | 11   | 3  | 242                                       |
| Hypotension<br>subjects affected / exposed   | 0 / 11 (0.00%)                             | 0 / 5 (0.00%)                                | 13 / 173 (7.51%)                          |
| occurrences (all)  | 0  | 0  | 18  |
| Surgical and medical procedures<br>Haemostasis<br>subjects affected / exposed  | 1 / 11 (9.09%)                             | 0 / 5 (0.00%)                                | 0 / 173 (0.00%)                           |
| occurrences (all)  | 1  | 0  | 0   |
| General disorders and administration<br>site conditions  |  |  |   |

|   |                 |                |                   |
|---|-----------------|----------------|-------------------|
| Chest pain                                      |                 |                |                   |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 1 / 5 (20.00%) | 9 / 173 (5.20%)   |
| occurrences (all)                               | 1               | 1              | 15                |
| Fatigue   |                 |                |                   |
| subjects affected / exposed                     | 4 / 11 (36.36%) | 2 / 5 (40.00%) | 55 / 173 (31.79%) |
| occurrences (all)                               | 7               | 2              | 121               |
| Pyrexia   |                 |                |                   |
| subjects affected / exposed                     | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 9 / 173 (5.20%)   |
| occurrences (all)                               | 2               | 0              | 10                |
| Asthenia  |                 |                |                   |
| subjects affected / exposed                     | 5 / 11 (45.45%) | 0 / 5 (0.00%)  | 41 / 173 (23.70%) |
| occurrences (all)                               | 6               | 0              | 67                |
| Mucosal inflammation                            |                 |                |                   |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 21 / 173 (12.14%) |
| occurrences (all)                               | 1               | 0              | 42                |
| Oedema peripheral                               |                 |                |                   |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 10 / 173 (5.78%)  |
| occurrences (all)                               | 1               | 0              | 15                |
| Reproductive system and breast disorders        |                 |                |                   |
| Breast mass                                     |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                               | 0               | 1              | 0                 |
| Respiratory, thoracic and mediastinal disorders |                 |                |                   |
| Cough   |                 |                |                   |
| subjects affected / exposed                     | 2 / 11 (18.18%) | 1 / 5 (20.00%) | 33 / 173 (19.08%) |
| occurrences (all)                               | 2               | 2              | 44                |
| Dysphonia                                       |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 37 / 173 (21.39%) |
| occurrences (all)                               | 0               | 0              | 49                |
| Dyspnoea  |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 24 / 173 (13.87%) |
| occurrences (all)                               | 0               | 0              | 32                |
| Pleural effusion                                |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 3 / 173 (1.73%)   |
| occurrences (all)                               | 0               | 0              | 3                 |
| Epistaxis                                       |                 |                |                   |

|   |                      |                     |                         |
|---|----------------------|---------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 7 / 173 (4.05%)<br>8    |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                          | 4 / 11 (36.36%)<br>5 | 0 / 5 (0.00%)<br>0  | 12 / 173 (6.94%)<br>20  |
| Dry throat<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Psychiatric disorders   |                      |                     |                         |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 11 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 10 / 173 (5.78%)<br>14  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 10 / 173 (5.78%)<br>13  |
| Investigations  |                      |                     |                         |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 11 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 19 / 173 (10.98%)<br>36 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 11 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 17 / 173 (9.83%)<br>27  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 11 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 7 / 173 (4.05%)<br>14   |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 11 (18.18%)<br>9 | 1 / 5 (20.00%)<br>2 | 14 / 173 (8.09%)<br>29  |
| Blood phosphorus decreased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 11 (9.09%)<br>2  | 1 / 5 (20.00%)<br>2 | 0 / 173 (0.00%)<br>0    |
| Blood thyroid stimulating hormone increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 17 / 173 (9.83%)<br>20  |
| Lipase increased  |                      |                     |                         |



|                                       |                 |                |                   |
|---------------------------------------|-----------------|----------------|-------------------|
| subjects affected / exposed           | 2 / 11 (18.18%) | 1 / 5 (20.00%) | 7 / 173 (4.05%)   |
| occurrences (all)                     | 5               | 1              | 25                |
| Weight decreased                      |                 |                |                   |
| subjects affected / exposed           | 4 / 11 (36.36%) | 1 / 5 (20.00%) | 70 / 173 (40.46%) |
| occurrences (all)                     | 13              | 1              | 198               |
| Amylase increased                     |                 |                |                   |
| subjects affected / exposed           | 3 / 11 (27.27%) | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                     | 4               | 2              | 0                 |
| Blood bicarbonate decreased           |                 |                |                   |
| subjects affected / exposed           | 1 / 11 (9.09%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                     | 3               | 1              | 0                 |
| Blood bilirubin increased             |                 |                |                   |
| subjects affected / exposed           | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                     | 3               | 0              | 0                 |
| Blood calcium increased               |                 |                |                   |
| subjects affected / exposed           | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                     | 1               | 0              | 0                 |
| Blood chloride increased              |                 |                |                   |
| subjects affected / exposed           | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                     | 1               | 0              | 0                 |
| Blood cholesterol increased           |                 |                |                   |
| subjects affected / exposed           | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                     | 0               | 1              | 0                 |
| Blood lactate dehydrogenase increased |                 |                |                   |
| subjects affected / exposed           | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                     | 0               | 1              | 0                 |
| Blood urea increased                  |                 |                |                   |
| subjects affected / exposed           | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                     | 0               | 1              | 0                 |
| Glomerular filtration rate decreased  |                 |                |                   |
| subjects affected / exposed           | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                     | 1               | 0              | 0                 |
| Creatinine renal clearance decreased  |                 |                |                   |
| subjects affected / exposed           | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                     | 3               | 0              | 0                 |

|  |                      |                     |                        |
|--|----------------------|---------------------|------------------------|
| Eosinophil count increased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 11 (9.09%)<br>2  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Haematocrit increased<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 11 (18.18%)<br>2 | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Haemoglobin increased<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Liver function test increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 11 (9.09%)<br>1  | 2 / 5 (40.00%)<br>2 | 0 / 173 (0.00%)<br>0   |
| International normalised ratio increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 173 (0.00%)<br>0   |
| Lymphocyte percentage decreased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 11 (0.00%)<br>0  | 1 / 5 (20.00%)<br>2 | 0 / 173 (0.00%)<br>0   |
| Protein total decreased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 11 (9.09%)<br>2  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Tri-iodothyronine free decreased<br>subjects affected / exposed<br>occurrences (all)         | 1 / 11 (9.09%)<br>3  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 11 (18.18%)<br>4 | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0   |
| Injury, poisoning and procedural complications   |                      |                     |                        |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 11 (9.09%)<br>2  | 0 / 5 (0.00%)<br>0  | 10 / 173 (5.78%)<br>12 |
| Mucosal excoriation  |                      |                     |                        |

|   |                      |                     |                         |
|---|----------------------|---------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                                | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)               | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Spinal compression fracture<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Nervous system disorders  |                      |                     |                         |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 11 (9.09%)<br>2  | 0 / 5 (0.00%)<br>0  | 14 / 173 (8.09%)<br>22  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 23 / 173 (13.29%)<br>42 |
| Dizziness exertional<br>subjects affected / exposed<br>occurrences (all)        | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 11 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 173 (0.00%)<br>0    |
| Blood and lymphatic system disorders  |                      |                     |                         |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 11 (18.18%)<br>8 | 2 / 5 (40.00%)<br>6 | 15 / 173 (8.67%)<br>30  |
| Anisocytosis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Macrocytosis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 11 (9.09%)<br>3  | 0 / 5 (0.00%)<br>0  | 0 / 173 (0.00%)<br>0    |
| Polychromasia   |                      |                     |                         |

|                             |                 |                |                   |
|-----------------------------|-----------------|----------------|-------------------|
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Thrombocytopenia            |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Thrombocytosis              |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Ear and labyrinth disorders |                 |                |                   |
| Tinnitus                    |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Eye disorders               |                 |                |                   |
| Vision blurred              |                 |                |                   |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)           | 0               | 6              | 0                 |
| Gastrointestinal disorders  |                 |                |                   |
| Abdominal pain              |                 |                |                   |
| subjects affected / exposed | 3 / 11 (27.27%) | 0 / 5 (0.00%)  | 17 / 173 (9.83%)  |
| occurrences (all)           | 7               | 0              | 72                |
| Abdominal pain upper        |                 |                |                   |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 32 / 173 (18.50%) |
| occurrences (all)           | 2               | 0              | 51                |
| Constipation                |                 |                |                   |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 5 (20.00%) | 17 / 173 (9.83%)  |
| occurrences (all)           | 2               | 1              | 25                |
| Diarrhoea                   |                 |                |                   |
| subjects affected / exposed | 6 / 11 (54.55%) | 2 / 5 (40.00%) | 88 / 173 (50.87%) |
| occurrences (all)           | 16              | 3              | 495               |
| Mouth ulceration            |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Nausea                      |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 38 / 173 (21.97%) |
| occurrences (all)           | 2               | 0              | 138               |
| Stomatitis                  |                 |                |                   |

|                                 |                 |                |                   |
|---------------------------------|-----------------|----------------|-------------------|
| subjects affected / exposed     | 2 / 11 (18.18%) | 1 / 5 (20.00%) | 20 / 173 (11.56%) |
| occurrences (all)               | 3               | 2              | 60                |
| Vomiting                        |                 |                |                   |
| subjects affected / exposed     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 38 / 173 (21.97%) |
| occurrences (all)               | 0               | 0              | 176               |
| Abdominal distension            |                 |                |                   |
| subjects affected / exposed     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 9 / 173 (5.20%)   |
| occurrences (all)               | 1               | 0              | 11                |
| Dry mouth                       |                 |                |                   |
| subjects affected / exposed     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 10 / 173 (5.78%)  |
| occurrences (all)               | 0               | 0              | 13                |
| Dyspepsia                       |                 |                |                   |
| subjects affected / exposed     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 13 / 173 (7.51%)  |
| occurrences (all)               | 1               | 0              | 15                |
| Flatulence                      |                 |                |                   |
| subjects affected / exposed     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 10 / 173 (5.78%)  |
| occurrences (all)               | 0               | 0              | 11                |
| Abdominal discomfort            |                 |                |                   |
| subjects affected / exposed     | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)               | 0               | 1              | 0                 |
| Anal fissure                    |                 |                |                   |
| subjects affected / exposed     | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)               | 0               | 1              | 0                 |
| Cheilitis                       |                 |                |                   |
| subjects affected / exposed     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)               | 1               | 0              | 0                 |
| Duodenitis                      |                 |                |                   |
| subjects affected / exposed     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)               | 1               | 0              | 0                 |
| Gastric ulcer                   |                 |                |                   |
| subjects affected / exposed     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)               | 1               | 0              | 0                 |
| Gingival bleeding               |                 |                |                   |
| subjects affected / exposed     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)               | 1               | 0              | 0                 |
| Gastroesophageal reflux disease |                 |                |                   |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Glossodynia                            |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Haematemesis                           |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Haemorrhoids                           |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Hiatus hernia                          |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Hyperchlorhydria                       |                 |                |                 |
| subjects affected / exposed            | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 2               | 0              | 0               |
| Melaena                                |                 |                |                 |
| subjects affected / exposed            | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 2               | 0              | 0               |
| Oesophagitis                           |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Oral disorder                          |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0               |
| Rectal haemorrhage                     |                 |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 4               | 0              | 0               |
| Toothache                              |                 |                |                 |
| subjects affected / exposed            | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%) |
| occurrences (all)                      | 2               | 0              | 0               |
| Upper gastrointestinal haemorrhage     |                 |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%) |
| occurrences (all)                      | 0               | 1              | 0               |
| Skin and subcutaneous tissue disorders |                 |                |                 |

|  |                 |                |                   |
|--|-----------------|----------------|-------------------|
| Alopecia                                   |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 1 / 5 (20.00%) | 6 / 173 (3.47%)   |
| occurrences (all)                          | 1               | 4              | 8                 |
| Palmar-plantar erythrodysesthesia syndrome |                 |                |                   |
| subjects affected / exposed                | 4 / 11 (36.36%) | 4 / 5 (80.00%) | 41 / 173 (23.70%) |
| occurrences (all)                          | 17              | 8              | 206               |
| Rash                                       |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 15 / 173 (8.67%)  |
| occurrences (all)                          | 2               | 0              | 19                |
| Erythema                                   |                 |                |                   |
| subjects affected / exposed                | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 5 / 173 (2.89%)   |
| occurrences (all)                          | 0               | 0              | 6                 |
| Pruritus                                   |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 1 / 5 (20.00%) | 7 / 173 (4.05%)   |
| occurrences (all)                          | 1               | 3              | 7                 |
| Skin exfoliation                           |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 3 / 173 (1.73%)   |
| occurrences (all)                          | 1               | 0              | 3                 |
| Blister                                    |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                          | 1               | 0              | 0                 |
| Dry skin                                   |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                          | 1               | 0              | 0                 |
| Pain of skin                               |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                          | 1               | 0              | 0                 |
| Eczema                                     |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                          | 1               | 0              | 0                 |
| Pigmentation disorder                      |                 |                |                   |
| subjects affected / exposed                | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                          | 1               | 0              | 0                 |
| Skin fissures                              |                 |                |                   |

|                             |                 |                |                   |
|-----------------------------|-----------------|----------------|-------------------|
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Rash erythematous           |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Skin hyperpigmentation      |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Skin mass                   |                 |                |                   |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)           | 0               | 1              | 0                 |
| Skin lesion                 |                 |                |                   |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 4               | 0              | 0                 |
| Skin toxicity               |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Skin ulcer                  |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 3               | 0              | 0                 |
| Renal and urinary disorders |                 |                |                   |
| Proteinuria                 |                 |                |                   |
| subjects affected / exposed | 6 / 11 (54.55%) | 0 / 5 (0.00%)  | 19 / 173 (10.98%) |
| occurrences (all)           | 34              | 0              | 63                |
| Chronic kidney disease      |                 |                |                   |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)           | 0               | 1              | 0                 |
| Dysuria                     |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 2               | 0              | 0                 |
| Haematuria                  |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |
| Pollakiuria                 |                 |                |                   |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)           | 1               | 0              | 0                 |



|   |                 |                |                   |
|---|-----------------|----------------|-------------------|
| Endocrine disorders                             |                 |                |                   |
| Hypothyroidism                                  |                 |                |                   |
| subjects affected / exposed                     | 3 / 11 (27.27%) | 0 / 5 (0.00%)  | 36 / 173 (20.81%) |
| occurrences (all)                               | 7               | 0              | 46                |
| Hyperthyroidism                                 |                 |                |                   |
| subjects affected / exposed                     | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                               | 2               | 0              | 0                 |
| Musculoskeletal and connective tissue disorders |                 |                |                   |
| Arthralgia                                      |                 |                |                   |
| subjects affected / exposed                     | 5 / 11 (45.45%) | 1 / 5 (20.00%) | 28 / 173 (16.18%) |
| occurrences (all)                               | 7               | 1              | 66                |
| Musculoskeletal pain                            |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 0 / 173 (0.00%)   |
| occurrences (all)                               | 0               | 1              | 0                 |
| Back pain                                       |                 |                |                   |
| subjects affected / exposed                     | 6 / 11 (54.55%) | 0 / 5 (0.00%)  | 29 / 173 (16.76%) |
| occurrences (all)                               | 11              | 0              | 52                |
| Pain in extremity                               |                 |                |                   |
| subjects affected / exposed                     | 4 / 11 (36.36%) | 0 / 5 (0.00%)  | 23 / 173 (13.29%) |
| occurrences (all)                               | 5               | 0              | 36                |
| Muscle spasms                                   |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 3 / 173 (1.73%)   |
| occurrences (all)                               | 0               | 0              | 7                 |
| Arthritis                                       |                 |                |                   |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                               | 2               | 0              | 0                 |
| Musculoskeletal chest pain                      |                 |                |                   |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 0 / 5 (0.00%)  | 7 / 173 (4.05%)   |
| occurrences (all)                               | 0               | 0              | 8                 |
| Flank pain                                      |                 |                |                   |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                               | 1               | 0              | 0                 |
| Gouty arthritis                                 |                 |                |                   |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)   |
| occurrences (all)                               | 6               | 0              | 0                 |
| Myalgia   |                 |                |                   |

|                                   |                 |                |                  |
|-----------------------------------|-----------------|----------------|------------------|
| subjects affected / exposed       | 4 / 11 (36.36%) | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 4               | 0              | 0                |
| Osteoarthritis                    |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 2               | 0              | 0                |
| Joint swelling                    |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |
| Periarthritis                     |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |
| Infections and infestations       |                 |                |                  |
| Nasopharyngitis                   |                 |                |                  |
| subjects affected / exposed       | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 10 / 173 (5.78%) |
| occurrences (all)                 | 2               | 0              | 10               |
| Upper respiratory tract infection |                 |                |                  |
| subjects affected / exposed       | 0 / 11 (0.00%)  | 1 / 5 (20.00%) | 14 / 173 (8.09%) |
| occurrences (all)                 | 0               | 1              | 18               |
| Urinary tract infection           |                 |                |                  |
| subjects affected / exposed       | 2 / 11 (18.18%) | 0 / 5 (0.00%)  | 10 / 173 (5.78%) |
| occurrences (all)                 | 2               | 0              | 15               |
| Haemorrhoid infection             |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |
| Pharyngotonsillitis               |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |
| Sinusitis                         |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |
| Rhinitis                          |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |
| Tooth infection                   |                 |                |                  |
| subjects affected / exposed       | 1 / 11 (9.09%)  | 0 / 5 (0.00%)  | 0 / 173 (0.00%)  |
| occurrences (all)                 | 1               | 0              | 0                |

|  |                      |                    |                         |
|--|----------------------|--------------------|-------------------------|
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0    |
| Metabolism and nutrition disorders                                     |                      |                    |                         |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 5 / 11 (45.45%)<br>5 | 0 / 5 (0.00%)<br>0 | 48 / 173 (27.75%)<br>85 |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)      | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0    |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)    | 1 / 11 (9.09%)<br>1  | 0 / 5 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0    |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 11 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 6 / 173 (3.47%)<br>12   |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all)     | 1 / 11 (9.09%)<br>2  | 0 / 5 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0    |

|   |                                    |  |  |
|---|------------------------------------|--|--|
| <b>Non-serious adverse events</b>   | Sorafenib (First-line<br>Subjects) |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 83 / 88 (94.32%)                   |  |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Anal neoplasm<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0                |  |  |
| Vascular disorders  |                                    |  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 28 / 88 (31.82%)<br>43             |  |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 3 / 88 (3.41%)<br>4                |  |  |
| Surgical and medical procedures   |                                    |  |  |
| Haemostasis   |                                    |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)        | 0 / 88 (0.00%)<br>0 |  |  |
| General disorders and administration<br>site conditions |                     |  |  |
| Chest pain  |                     |  |  |
| subjects affected / exposed                             | 7 / 88 (7.95%)      |  |  |
| occurrences (all)                                       | 7                   |  |  |
| Fatigue   |                     |  |  |
| subjects affected / exposed                             | 25 / 88 (28.41%)    |  |  |
| occurrences (all)                                       | 33                  |  |  |
| Pyrexia   |                     |  |  |
| subjects affected / exposed                             | 4 / 88 (4.55%)      |  |  |
| occurrences (all)                                       | 4                   |  |  |
| Asthenia  |                     |  |  |
| subjects affected / exposed                             | 15 / 88 (17.05%)    |  |  |
| occurrences (all)                                       | 20                  |  |  |
| Mucosal inflammation                                    |                     |  |  |
| subjects affected / exposed                             | 9 / 88 (10.23%)     |  |  |
| occurrences (all)                                       | 11                  |  |  |
| Oedema peripheral                                       |                     |  |  |
| subjects affected / exposed                             | 4 / 88 (4.55%)      |  |  |
| occurrences (all)                                       | 5                   |  |  |
| Reproductive system and breast<br>disorders             |                     |  |  |
| Breast mass   |                     |  |  |
| subjects affected / exposed                             | 0 / 88 (0.00%)      |  |  |
| occurrences (all)                                       | 0                   |  |  |
| Respiratory, thoracic and mediastinal<br>disorders      |                     |  |  |
| Cough   |                     |  |  |
| subjects affected / exposed                             | 14 / 88 (15.91%)    |  |  |
| occurrences (all)                                       | 22                  |  |  |
| Dysphonia   |                     |  |  |
| subjects affected / exposed                             | 10 / 88 (11.36%)    |  |  |
| occurrences (all)                                       | 10                  |  |  |
| Dyspnoea  |                     |  |  |
| subjects affected / exposed                             | 11 / 88 (12.50%)    |  |  |
| occurrences (all)                                       | 14                  |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)                                     | 5 / 88 (5.68%)<br>5  |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 5 / 88 (5.68%)<br>5  |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                   | 5 / 88 (5.68%)<br>5  |  |  |
| Dry throat<br>subjects affected / exposed<br>occurrences (all)   | 0 / 88 (0.00%)<br>0  |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 88 (0.00%)<br>0  |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 5 / 88 (5.68%)<br>5  |  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 8 / 88 (9.09%)<br>14 |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                 | 8 / 88 (9.09%)<br>12 |  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                 | 6 / 88 (6.82%)<br>7  |  |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                           | 6 / 88 (6.82%)<br>7  |  |  |
| Blood phosphorus decreased<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 88 (0.00%)<br>0  |  |  |
| Blood thyroid stimulating hormone increased  |                      |  |  |

|                                       |                  |  |  |
|---------------------------------------|------------------|--|--|
| subjects affected / exposed           | 2 / 88 (2.27%)   |  |  |
| occurrences (all)                     | 2                |  |  |
| Lipase increased                      |                  |  |  |
| subjects affected / exposed           | 5 / 88 (5.68%)   |  |  |
| occurrences (all)                     | 9                |  |  |
| Weight decreased                      |                  |  |  |
| subjects affected / exposed           | 24 / 88 (27.27%) |  |  |
| occurrences (all)                     | 63               |  |  |
| Amylase increased                     |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood bicarbonate decreased           |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood bilirubin increased             |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood calcium increased               |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood chloride increased              |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood cholesterol increased           |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood lactate dehydrogenase increased |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Blood urea increased                  |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |
| Glomerular filtration rate decreased  |                  |  |  |
| subjects affected / exposed           | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                     | 0                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Creatinine renal clearance decreased           |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Eosinophil count increased                     |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Haematocrit increased                          |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Haemoglobin decreased                          |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Haemoglobin increased                          |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Liver function test increased                  |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| International normalised ratio increased       |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Lymphocyte percentage decreased                |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Protein total decreased                        |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Tri-iodothyronine free decreased               |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Blood pressure increased                       |                |  |  |
| subjects affected / exposed                    | 0 / 88 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Injury, poisoning and procedural complications |                |  |  |

|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| Fall                                 |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Mucosal excoriation                  |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Skin abrasion                        |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Spinal compression fracture          |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Nervous system disorders             |                 |  |  |
| Dizziness                            |                 |  |  |
| subjects affected / exposed          | 2 / 88 (2.27%)  |  |  |
| occurrences (all)                    | 3               |  |  |
| Headache                             |                 |  |  |
| subjects affected / exposed          | 6 / 88 (6.82%)  |  |  |
| occurrences (all)                    | 7               |  |  |
| Dizziness exertional                 |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Dysaesthesia                         |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Neuralgia                            |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood and lymphatic system disorders |                 |  |  |
| Anaemia                              |                 |  |  |
| subjects affected / exposed          | 9 / 88 (10.23%) |  |  |
| occurrences (all)                    | 19              |  |  |
| Anisocytosis                         |                 |  |  |
| subjects affected / exposed          | 0 / 88 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Macrocytosis                         |                 |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Polychromasia               |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Thrombocytopenia            |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Thrombocytosis              |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Ear and labyrinth disorders |                  |  |  |
| Tinnitus                    |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Eye disorders               |                  |  |  |
| Vision blurred              |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Gastrointestinal disorders  |                  |  |  |
| Abdominal pain              |                  |  |  |
| subjects affected / exposed | 8 / 88 (9.09%)   |  |  |
| occurrences (all)           | 11               |  |  |
| Abdominal pain upper        |                  |  |  |
| subjects affected / exposed | 7 / 88 (7.95%)   |  |  |
| occurrences (all)           | 9                |  |  |
| Constipation                |                  |  |  |
| subjects affected / exposed | 10 / 88 (11.36%) |  |  |
| occurrences (all)           | 12               |  |  |
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 34 / 88 (38.64%) |  |  |
| occurrences (all)           | 170              |  |  |
| Mouth ulceration            |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Nausea                      |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 15 / 88 (17.05%) |  |  |
| occurrences (all)           | 22               |  |  |
| Stomatitis                  |                  |  |  |
| subjects affected / exposed | 4 / 88 (4.55%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Vomiting                    |                  |  |  |
| subjects affected / exposed | 11 / 88 (12.50%) |  |  |
| occurrences (all)           | 29               |  |  |
| Abdominal distension        |                  |  |  |
| subjects affected / exposed | 1 / 88 (1.14%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Dry mouth                   |                  |  |  |
| subjects affected / exposed | 1 / 88 (1.14%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Dyspepsia                   |                  |  |  |
| subjects affected / exposed | 3 / 88 (3.41%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Flatulence                  |                  |  |  |
| subjects affected / exposed | 3 / 88 (3.41%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Abdominal discomfort        |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Anal fissure                |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Cheilitis                   |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Duodenitis                  |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Gastric ulcer               |                  |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Gingival bleeding           |                  |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Gastrooesophageal reflux disease   |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Glossodynia                        |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Haematemesis                       |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Haemorrhoids                       |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Hiatus hernia                      |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Hyperchlorhydria                   |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Melaena                            |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Oesophagitis                       |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Oral disorder                      |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Rectal haemorrhage                 |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Toothache                          |                |  |  |
| subjects affected / exposed        | 0 / 88 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Upper gastrointestinal haemorrhage |                |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                 | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Skin and subcutaneous tissue disorders      |                  |  |  |
| Alopecia                                    |                  |  |  |
| subjects affected / exposed                 | 17 / 88 (19.32%) |  |  |
| occurrences (all)                           | 20               |  |  |
| Palmar-plantar erythrodysaesthesia syndrome |                  |  |  |
| subjects affected / exposed                 | 31 / 88 (35.23%) |  |  |
| occurrences (all)                           | 79               |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                 | 18 / 88 (20.45%) |  |  |
| occurrences (all)                           | 27               |  |  |
| Erythema                                    |                  |  |  |
| subjects affected / exposed                 | 21 / 88 (23.86%) |  |  |
| occurrences (all)                           | 27               |  |  |
| Pruritus                                    |                  |  |  |
| subjects affected / exposed                 | 9 / 88 (10.23%)  |  |  |
| occurrences (all)                           | 13               |  |  |
| Skin exfoliation                            |                  |  |  |
| subjects affected / exposed                 | 6 / 88 (6.82%)   |  |  |
| occurrences (all)                           | 7                |  |  |
| Blister                                     |                  |  |  |
| subjects affected / exposed                 | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Dry skin                                    |                  |  |  |
| subjects affected / exposed                 | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Pain of skin                                |                  |  |  |
| subjects affected / exposed                 | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Eczema                                      |                  |  |  |
| subjects affected / exposed                 | 0 / 88 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Pigmentation disorder                       |                  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Skin fissures               |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Rash erythematous           |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Skin hyperpigmentation      |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Skin mass                   |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Skin lesion                 |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Skin toxicity               |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Skin ulcer                  |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Renal and urinary disorders |                 |  |  |
| Proteinuria                 |                 |  |  |
| subjects affected / exposed | 9 / 88 (10.23%) |  |  |
| occurrences (all)           | 11              |  |  |
| Chronic kidney disease      |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Dysuria                     |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Haematuria                  |                 |  |  |
| subjects affected / exposed | 0 / 88 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                | 0 / 88 (0.00%)<br>0    |  |  |
| Endocrine disorders  |                        |  |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)             | 5 / 88 (5.68%)<br>5    |  |  |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)            | 0 / 88 (0.00%)<br>0    |  |  |
| Musculoskeletal and connective tissue disorders                                |                        |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 10 / 88 (11.36%)<br>18 |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 0 / 88 (0.00%)<br>0    |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 14 / 88 (15.91%)<br>17 |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 6 / 88 (6.82%)<br>8    |  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)              | 6 / 88 (6.82%)<br>8    |  |  |
| Arthritis<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 88 (0.00%)<br>0    |  |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 5 / 88 (5.68%)<br>6    |  |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 88 (0.00%)<br>0    |  |  |
| Gouty arthritis  |                        |  |  |

|                                   |                |  |  |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Myalgia                           |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Osteoarthritis                    |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Joint swelling                    |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Periarthritis                     |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Infections and infestations       |                |  |  |
| Nasopharyngitis                   |                |  |  |
| subjects affected / exposed       | 3 / 88 (3.41%) |  |  |
| occurrences (all)                 | 5              |  |  |
| Upper respiratory tract infection |                |  |  |
| subjects affected / exposed       | 1 / 88 (1.14%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Urinary tract infection           |                |  |  |
| subjects affected / exposed       | 4 / 88 (4.55%) |  |  |
| occurrences (all)                 | 5              |  |  |
| Haemorrhoid infection             |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Pharyngotonsillitis               |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Sinusitis                         |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Rhinitis                          |                |  |  |
| subjects affected / exposed       | 0 / 88 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0    |  |  |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0    |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 16 / 88 (18.18%)<br>21 |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0    |  |  |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0    |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)   | 5 / 88 (5.68%)<br>9    |  |  |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 88 (0.00%)<br>0    |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

|   |
|---|
| Objective of statistical analysis for secondary endpoints: summarize data using descriptive statistics without performing hypothesis testing. All subjects from sites in China are excluded from updated safety reporting due to lack of HGRAC filings. |
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Notes: