



## Clinical trial results:

### A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-002992-33    |
| Trial protocol           | IT DE GB ES PL BE |
| Global end of trial date | 10 March 2021     |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v2 (current)      |
| This version publication date  | 24 March 2022     |
| First version publication date | 12 September 2018 |
| Version creation reason        |                   |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | E7080-G000-304 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01761266 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                   |
|------------------------------|-----------------------------------------------------------------------------------|
| Sponsor organisation name    | Eisai, Inc.                                                                       |
| Sponsor organisation address | 155 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677              |
| Public contact               | Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com  |
| Scientific contact           | Eisai Medical Information, Eisai, Inc., +1 888-274-2378, esi_oncmedinfo@eisai.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                       | 10 March 2021 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 10 March 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to compare overall survival (OS) in subjects treated with lenvatinib versus sorafenib as a first-line treatment in subjects with unresectable hepatocellular carcinoma (HCC).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 01 March 2013 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | China: 213              |
| Country: Number of subjects enrolled | Hong Kong: 21           |
| Country: Number of subjects enrolled | Japan: 168              |
| Country: Number of subjects enrolled | Korea, Republic of: 142 |
| Country: Number of subjects enrolled | Malaysia: 11            |
| Country: Number of subjects enrolled | Philippines: 7          |
| Country: Number of subjects enrolled | Singapore: 16           |
| Country: Number of subjects enrolled | Taiwan: 54              |
| Country: Number of subjects enrolled | Thailand: 8             |
| Country: Number of subjects enrolled | Belgium: 4              |
| Country: Number of subjects enrolled | Canada: 1               |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | France: 52             |
| Country: Number of subjects enrolled | Germany: 20            |
| Country: Number of subjects enrolled | Israel: 3              |
| Country: Number of subjects enrolled | Italy: 28              |
| Country: Number of subjects enrolled | Poland: 35             |
| Country: Number of subjects enrolled | Russian Federation: 73 |
| Country: Number of subjects enrolled | Spain: 15              |
| Country: Number of subjects enrolled | United Kingdom: 20     |
| Country: Number of subjects enrolled | United States: 63      |
| Worldwide total number of subjects   | 954                    |
| EEA total number of subjects         | 154                    |

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)                      | 553 |
| From 65 to 84 years                       | 397 |
| 85 years and over                         | 4   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects took part in the study at 154 investigative sites in Australia, Belgium, Canada, China, France, Germany, Hong Kong, Israel, Italy, Japan, South Korea, Malaysia, Philippines, Poland, Russia, Singapore, Spain, Taiwan, Thailand, United Kingdom, and the United States from 1 March 2013 to 10 March 2021.

### Pre-assignment

Screening details:

A total of 1,492 subjects were screened, 954 subjects were enrolled and randomized, out of which 951 subjects were treated in the study.

### Period 1

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

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Lenvatinib |

Arm description:

Subjects received lenvatinib capsules 12 milligram (mg) based on the subject's body weight greater than or equal to ( $\geq$ ) 60 kilogram (kg) or 8 mg based on the subject's body weight less than ( $<$ ) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Lenvatinib   |
| Investigational medicinal product code | E7080        |
| Other name                             | Lenvima      |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Lenvatinib capsule 12 mg based on the subject's body weight  $\geq 60$  kg or 8 mg based on the subject's body weight  $< 60$  kg at baseline, orally, QD in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Sorafenib |
|------------------|-----------|

Arm description:

Subjects received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

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

Dosage and administration details:

Sorafenib 400 mg tablets, orally, BID in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

| <b>Number of subjects in period 1</b> | Lenvatinib | Sorafenib |
|---------------------------------------|------------|-----------|
| Started                               | 478        | 476       |
| Treated                               | 476        | 475       |
| Completed                             | 0          | 0         |
| Not completed                         | 478        | 476       |
| Consent withdrawn by subject          | 14         | 10        |
| Death                                 | 415        | 402       |
| Sponsor Decision                      | 41         | 52        |
| Lost to follow-up                     | 8          | 12        |

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Lenvatinib |
|-----------------------|------------|

Reporting group description:

Subjects received lenvatinib capsules 12 milligram (mg) based on the subject's body weight greater than or equal to ( $\geq$ ) 60 kilogram (kg) or 8 mg based on the subject's body weight less than ( $<$ ) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Sorafenib |
|-----------------------|-----------|

Reporting group description:

Subjects received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

| Reporting group values | Lenvatinib | Sorafenib | Total |
|------------------------|------------|-----------|-------|
| Number of subjects     | 478        | 476       | 954   |
| Age categorical        |            |           |       |
| Units: Subjects        |            |           |       |

|                                           |             |             |     |
|-------------------------------------------|-------------|-------------|-----|
| Age Continuous                            |             |             |     |
| Units: years                              |             |             |     |
| arithmetic mean                           | 61.3        | 61.2        |     |
| standard deviation                        | $\pm 11.69$ | $\pm 12.01$ | -   |
| Sex: Female, Male                         |             |             |     |
| Units: subjects                           |             |             |     |
| Female                                    | 73          | 75          | 148 |
| Male                                      | 405         | 401         | 806 |
| Ethnicity (NIH/OMB)                       |             |             |     |
| Units: Subjects                           |             |             |     |
| Hispanic or Latino                        | 6           | 11          | 17  |
| Not Hispanic or Latino                    | 472         | 465         | 937 |
| Unknown or Not Reported                   | 0           | 0           | 0   |
| Race (NIH/OMB)                            |             |             |     |
| Units: Subjects                           |             |             |     |
| American Indian or Alaska Native          | 1           | 0           | 1   |
| Asian                                     | 334         | 326         | 660 |
| Native Hawaiian or Other Pacific Islander | 0           | 1           | 1   |
| Black or African American                 | 7           | 6           | 13  |
| White                                     | 135         | 141         | 276 |
| Other                                     | 1           | 2           | 3   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                      |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                | Lenvatinib |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                         |            |
| Subjects received lenvatinib capsules 12 milligram (mg) based on the subject's body weight greater than or equal to ( $\geq$ ) 60 kilogram (kg) or 8 mg based on the subject's body weight less than ( $<$ ) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent. |            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                | Sorafenib  |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                         |            |
| Subjects received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.                                                                                                                                                                                   |            |

### Primary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                                              |                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                              | Overall Survival (OS) <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                       |                                      |
| OS was defined as the duration from the date of randomization until the date of death from any cause. Subjects who were lost to follow-up were censored at the last date the subject was known to be alive, and subjects who remained alive were censored at the time of data cutoff. The full analysis set (FAS) included all subjects who were randomized. |                                      |
| End point type                                                                                                                                                                                                                                                                                                                                               | Primary                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                         |                                      |
| From date of randomization until date of death from any cause (approximately up to 3.8 years)                                                                                                                                                                                                                                                                |                                      |
| Notes:                                                                                                                                                                                                                                                                                                                                                       |                                      |
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.                                                                                                                                                                                          |                                      |
| Justification: No statistical analysis was planned for this endpoint.                                                                                                                                                                                                                                                                                        |                                      |

| End point values                 | Lenvatinib          | Sorafenib           |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 478                 | 476                 |  |  |
| Units: months                    |                     |                     |  |  |
| median (confidence interval 95%) | 13.6 (12.1 to 14.9) | 12.3 (10.4 to 13.9) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Progression Free Survival (PFS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                 |
| PFS was defined as the time from the date of randomization to the date of first documentation of disease progression based on modified Response Evaluation Criteria in Solid Tumors (mRECIST), or date of death, whichever occurred first. Disease progression was defined as at least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized. |                                 |

|                                                                                                                                                                      |           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                                       | Secondary |
| End point timeframe:                                                                                                                                                 |           |
| From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years) |           |

| End point values                 | Lenvatinib       | Sorafenib        |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 478              | 476              |  |  |
| Units: months                    |                  |                  |  |  |
| median (confidence interval 95%) | 7.4 (6.9 to 8.8) | 3.7 (3.6 to 4.6) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Progression (TTP)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Time to Progression (TTP) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                           |
| TTP was defined as the time from the date of randomization to the date of first documentation of disease progression based on mRECIST. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized. |                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                           |
| The time from the date of randomization to the date of first documentation of disease progression (approximately up to 3.8 years)                                                                                                                                                                                                                                                                                                                                               |                           |

| End point values                 | Lenvatinib       | Sorafenib        |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 478              | 476              |  |  |
| Units: months                    |                  |                  |  |  |
| median (confidence interval 95%) | 8.9 (7.4 to 9.2) | 3.7 (3.6 to 5.4) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR)

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



or partial response (PR) based on mRECIST. CR was defined as disappearance of any intratumoral arterial enhancement in all target lesions. PR was defined as at least a 30% decrease in the sum of diameters of viable (enhancement of arterial phase) target lesions taking as reference to the baseline sum of the diameters of target lesions. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

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

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

| End point values                 | Lenvatinib          | Sorafenib         |  |  |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type               | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed      | 478                 | 476               |  |  |
| Units: percentage of subjects    |                     |                   |  |  |
| number (confidence interval 95%) | 24.1 (20.2 to 27.9) | 9.2 (6.6 to 11.8) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Clinically Meaningful Worsening of Health Related Quality of Life (HRQoL) Assessed Using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to Clinically Meaningful Worsening of Health Related Quality of Life (HRQoL) Assessed Using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

EORTC QLQ-C30 included 30 questions comprising 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social) and 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnoea, appetite loss, insomnia, constipation, diarrhea and financial difficulties) and a single global health and QOL status score. Most questions used a 4-point scale (1=Not at all to 4=Very much); 2 questions used a 7-point scale (1= Very poor to 7=Excellent). All domain scores were calculated as an average of item scores and transformed to 0 to 100 score range. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/quality of life (QoL) represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problem. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

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

End point timeframe:

Baseline up to Off-Treatment Visit (approximately up to 3.8 years)

| End point values                 | Lenvatinib         | Sorafenib          |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 478                | 476                |  |  |
| Units: months                    |                    |                    |  |  |
| median (confidence interval 95%) | 1.7 (1.05 to 1.84) | 1.8 (1.05 to 1.84) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Clinically Meaningful Worsening of HRQoL Assessed Using - EORTC QLQ- Hepatocellular Carcinoma Domain (HCC 18)

|                 |                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| End point title | Time to Clinically Meaningful Worsening of HRQoL Assessed Using - EORTC QLQ- Hepatocellular Carcinoma Domain (HCC 18) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|

End point description:

The EORTC QLQ-HCC-18 was an 18-item questionnaire design used along with the 30-item EORTC QLQ-C30. EORTC QLQ-HCC 18 questionnaire included 8 symptom scales such as fatigue, jaundice, body image, nutrition, pain, fever, sex life and abdominal swelling. Each individual item ranges from 1 to 4, where 1 = "not at all" and 4 = "very much." All domain scores were calculated as an average of item scores and transformed to 0 to 100 score range. A high score for a functional scale represented a high/healthy level of functioning, a high score for the global health status/quality of life (QoL) represented a high QoL, but a high score for a symptom scale/item represented a high level of symptomatology/problem. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

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

End point timeframe:

Baseline up to Off-Treatment Visit (approximately up to 3.8 years)

| End point values                 | Lenvatinib         | Sorafenib           |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 478                | 476                 |  |  |
| Units: months                    |                    |                     |  |  |
| median (confidence interval 95%) |                    |                     |  |  |
| Fatigue                          | 1.9 (1.81 to 1.97) | 1.8 (1.74 to 1.87)  |  |  |
| Jaundice                         | 4.6 (3.72 to 5.52) | 3.7 (2.86 to 4.73)  |  |  |
| Body Image                       | 2.8 (2.73 to 3.68) | 1.9 (1.84 to 2.73)  |  |  |
| Nutrition                        | 4.1 (3.68 to 5.52) | 2.8 (2.04 to 3.06)  |  |  |
| Pain                             | 2.7 (1.97 to 2.83) | 2.8 (2.73 to 3.72)  |  |  |
| Fever                            | 5.5 (4.57 to 6.51) | 3.7 (2.99 to 5.52)  |  |  |
| Sex Life                         | 7.4 (5.46 to 9.17) | 6.7 (4.60 to 13.78) |  |  |
| Abdominal swelling               | 7.4 (5.52 to 9.24) | 7.4 (5.46 to 10.13) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Clinically Meaningful Worsening of HRQoL Assessed Using EuroQol Five Dimension Health Questionnaire (EQ-5D-3L)

|                 |                                                                                                                        |
|-----------------|------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to Clinically Meaningful Worsening of HRQoL Assessed Using EuroQol Five Dimension Health Questionnaire (EQ-5D-3L) |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

#### End point description:

The EuroQol five dimension health questionnaire (EQ-5D-3L) assesses quality of life along 5 dimensions. Subjects rate 5 aspects of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). The summed score ranges from 3-15 with "3" corresponding to no problems; "15" corresponding to severe problems in 5 dimensions. EQ-5D-3L also included EQ visual analogue scale (VAS) that ranges between 100 (best imaginable health); 0 (worst imaginable health). Decrease from baseline in EQ-5D-3L signifies improvement. Total index EQ-5D-3L summary score weighted with range -0.594 (worst) to 1.0 (best). EQ-5D-3L also included EQ health utilities index (HUI) where 1.00 indicated perfect health while score of 0.00 indicated death. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

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

#### End point timeframe:

Baseline up to Off-Treatment Visit (approximately up to 3.8 years)

| End point values                 | Lenvatinib         | Sorafenib          |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 478                | 476                |  |  |
| Units: months                    |                    |                    |  |  |
| median (confidence interval 95%) |                    |                    |  |  |
| VAS                              | 2.8 (2.17 to 3.65) | 1.9 (1.84 to 2.33) |  |  |
| HUI                              | 2.8 (1.97 to 3.52) | 1.9 (1.84 to 2.66) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib |
|-----------------|--------------------------------------------------------------------------|

End point description:

AUC was assessed on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 1 Day 15. Summarized data for all time points was reported. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The pharmacokinetic (PK) analysis set included all subjects who had received at least 1 dose of lenvatinib and had at least 1 quantifiable lenvatinib concentration.

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

End point timeframe:

Cycle 1 Day 1, Cycle 2 Day 1: pre-dose, 0.5-4 and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 2-12 hours post-dose (cycle length= 28 days)

| End point values                              | Lenvatinib       | Sorafenib        |  |  |
|-----------------------------------------------|------------------|------------------|--|--|
| Subject group type                            | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed                   | 150              | 318              |  |  |
| Units: nanogram*hour per milliliter (ng*h/mL) |                  |                  |  |  |
| arithmetic mean (standard deviation)          | 1969.6 (± 743.0) | 2120.9 (± 685.6) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Disease control rate (DCR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Disease control rate (DCR) |
|-----------------|----------------------------|

End point description:

DCR was defined as the percentage of subjects with a best overall response of CR or PR, or stable disease (SD). Best overall response of SD must have been  $\geq 7$  weeks after randomization. CR was defined as disappearance of any intratumoral arterial enhancement in all target lesions. PR was defined as at least a 30% decrease in the sum of diameters of viable (enhancement of arterial phase) target lesions taking as reference the baseline sum of the diameters of target lesions. SD was when a case does not qualify for either PR or PD and was new non-target lesions. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this pre-specified endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

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

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

| End point values                 | Lenvatinib          | Sorafenib           |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 478                 | 476                 |  |  |
| Units: percentage of subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 75.5 (71.7 to 79.4) | 60.5 (56.1 to 64.9) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Clinical Benefit Rate (CBR)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Clinical Benefit Rate (CBR) |
|-----------------|-----------------------------|

End point description:

CBR was defined as percentage of subjects with best overall response of CR or PR or durable SD (duration of SD  $\geq$  23 weeks after randomization). For subjects whose best overall response (BOR) was SD, duration of SD was defined as time from date of randomization to first documented PD or death, whichever occurred first. CR was defined as disappearance of any intratumoral arterial enhancement in all target lesions. PR was defined as at least a 30% decrease in the sum of diameters of viable (enhancement of arterial phase) target lesions taking as reference baseline sum of diameters of target lesions. SD was when a case does not qualify for either PR or PD. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this pre-specified endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

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

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

| End point values                 | Lenvatinib          | Sorafenib           |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 478                 | 476                 |  |  |
| Units: percentage of subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 59.0 (54.6 to 63.4) | 38.4 (34.1 to 42.8) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percent Change from Baseline in Serum Biomarker

|                 |                                                 |
|-----------------|-------------------------------------------------|
| End point title | Percent Change from Baseline in Serum Biomarker |
|-----------------|-------------------------------------------------|

End point description:

The serum biomarkers analysed were angiopoietin-2 (ANG2), fibroblast growth factor 19 (FGF19), fibroblast growth factor 21 (FGF21), fibroblast growth factor 23 (FGF23) and vascular endothelial growth factor (VEGF) as blood serum biomarkers, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) as a blood tumor marker in serum. As planned, data for this pre-specified endpoint was collected and analyzed up to the primary completion date. The pharmacodynamics (PD) analysis set included all subjects who received at least 1 dose of study drug and had evaluable PD data. Here "n" was subjects who were evaluable for the outcome measure at given time points.

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

End point timeframe:

Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 7 Day 1, Cycle 8 Day 1, Cycle 9 Day 1 and at the Off-Treatment Visit (approximately up to 3.8 years)

| End point values            | Lenvatinib       | Sorafenib       |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 66               | 48              |  |  |
| Units: percent change       |                  |                 |  |  |
| median (standard deviation) |                  |                 |  |  |
| ANG 2: Cycle 1 Day 15       | -28.1 (± 15.94)  | 8.9 (± 23.96)   |  |  |
| ANG 2: Cycle 2 Day 1        | -28.8 (± 16.53)  | -0.9 (± 24.06)  |  |  |
| ANG 2: Cycle 3 Day 1        | -32.2 (± 23.23)  | 0.5 (± 26.62)   |  |  |
| ANG 2: Cycle 4 Day 1        | -35.6 (± 22.91)  | -4.5 (± 20.05)  |  |  |
| ANG 2: Cycle 5 Day 1        | -38.9 (± 19.83)  | 7.0 (± 23.25)   |  |  |
| ANG 2: Cycle 6 Day 1        | -36.7 (± 23.59)  | -3.6 (± 24.82)  |  |  |
| ANG 2: Cycle 7 Day 1        | -41.4 (± 21.20)  | 1.0 (± 32.83)   |  |  |
| ANG 2: Cycle 8 Day 1        | -40.2 (± 25.33)  | -6.7 (± 31.26)  |  |  |
| ANG 2: Cycle 9 Day 1        | -39.6 (± 14.04)  | -1.1 (± 29.68)  |  |  |
| ANG 2: Off-Treatment        | 11.7 (± 99.13)   | 16.8 (± 27.88)  |  |  |
| FGF19: Cycle 1 Day 15       | 75.0 (± 155.01)  | 1.3 (± 83.65)   |  |  |
| FGF19: Cycle 2 Day 1        | 66.5 (± 134.26)  | 36.6 (± 119.65) |  |  |
| FGF19: Cycle 3 Day 1        | 86.9 (± 123.85)  | 22.8 (± 70.58)  |  |  |
| FGF19: Cycle 4 Day 1        | 208.1 (± 602.11) | 46.8 (± 214.14) |  |  |
| FGF19: Cycle 5 Day 1        | 152.8 (± 228.37) | -1.0 (± 40.36)  |  |  |
| FGF19: Cycle 6 Day 1        | 119.8 (± 203.81) | 26.9 (± 67.13)  |  |  |
| FGF19: Cycle 7 Day 1        | 64.4 (± 101.97)  | -5.9 (± 57.39)  |  |  |
| FGF19: Cycle 8 Day 1        | 95.8 (± 135.31)  | 53.9 (± 113.79) |  |  |
| FGF19: Cycle 9 Day 1        | 159.3 (± 202.00) | 56.6 (± 109.46) |  |  |
| FGF19: Off-Treatment        | 140.1 (± 270.73) | 9.0 (± 64.17)   |  |  |
| FGF 21: Cycle 1 Day 15      | 22.0 (± 75.22)   | 4.0 (± 43.14)   |  |  |
| FGF 21: Cycle 2 Day 1       | 15.7 (± 77.44)   | 18.6 (± 57.18)  |  |  |
| FGF 21: Cycle 3 Day 1       | 38.3 (± 38.3)    | 49.4 (± 76.43)  |  |  |
| FGF 21: Cycle 4 Day 1       | 42.9 (± 145.43)  | 32.8 (± 70.63)  |  |  |
| FGF 21: Cycle 5 Day 1       | 41.0 (± 95.97)   | 31.1 (± 43.15)  |  |  |
| FGF 21: Cycle 6 Day 1       | 52.6 (± 168.22)  | 23.2 (± 40.90)  |  |  |

|                          |                   |                   |  |  |
|--------------------------|-------------------|-------------------|--|--|
| FGF 21: Cycle 7 Day 1    | 63.4 (± 128.34)   | 23.7 (± 53.84)    |  |  |
| FGF 21 : Cycle 8 Day1    | 38.3 (± 115.53)   | 17.0 (± 68.51)    |  |  |
| FGF 21: Cycle 9 Day1     | 59.1 (± 108.39)   | 68.9 (± 103.55)   |  |  |
| FGF 21: Off-Treatment    | 141.4 (± 340.51)  | 104.9 (± 183.28)  |  |  |
| FGF 23: Cycle 1 Day15    | 23.9 (± 49.01)    | -16.3 (± 36.14)   |  |  |
| FGF 23: Cycle 2 Day 1    | 20.9 (± 56.91)    | -6.2 (± 48.18)    |  |  |
| FGF 23: Cycle 3 Day 1    | 25.5 (± 45.27)    | 17.3 (± 75.25)    |  |  |
| FGF 23: Cycle 4 Day 1    | 29.5 (± 48.38)    | 14.2 (± 49.29)    |  |  |
| FGF 23: Cycle 5 Day 1    | 29.6 (± 63.69)    | 1.0 (± 47.28)     |  |  |
| FGF 23: Cycle 6 Day 1    | 26.3 (± 54.57)    | -10.6 (± 46.15)   |  |  |
| FGF 23: Cycle 7 Day 1    | 31.5 (± 57.44)    | 0.7 (± 46.95)     |  |  |
| FGF 23: Cycle 8 Day 1    | 38.1 (± 67.35)    | 2.8 (± 43.84)     |  |  |
| FGF 23: Cycle 9 Day 1    | 23.2 (± 62.58)    | 0.5 (± 38.74)     |  |  |
| FGF 23: Off-Treatment    | 17.8 (± 73.59)    | 14.2 (± 47.11)    |  |  |
| PIVKA-II: Cycle 1 Day 15 | 80.0 (± 171.41)   | 166.9 (± 256.04)  |  |  |
| PIVKA-II: Cycle 2 Day 1  | 169.7 (± 329.33)  | 243.8 (± 416.82)  |  |  |
| PIVKA-II: Cycle 3 Day 1  | 252.4 (± 611.40)  | 218.7 (± 281.45)  |  |  |
| PIVKA-II: Cycle 4 Day 1  | 371.7 (± 812.45)  | 196.2 (± 348.80)  |  |  |
| PIVKA-II: Cycle 5 Day 1  | 628.2 (± 1752.64) | 369.5 (± 766.59)  |  |  |
| PIVKA-II: Cycle 6 Day 1  | 648.7 (± 2746.41) | 415.7 (± 554.27)  |  |  |
| PIVKA-II: Cycle 7 Day 1  | 184.8 (± 352.75)  | 703.6 (± 1226.58) |  |  |
| PIVKA-II: Cycle 8 Day 1  | 277.8 (± 481.53)  | 724.0 (± 1257.87) |  |  |
| PIVKA-II: Cycle 9 Day 1  | 318.8 (± 577.21)  | 859.1 (± 1492.93) |  |  |
| PIVKA-II: Off-Treatment  | 809.3 (± 1827.42) | 272.5 (± 489.60)  |  |  |
| VEGF: Cycle 1 Day 15     | 157.5 (± 300.21)  | 97.4 (± 118.43)   |  |  |
| VEGF: Cycle 2 Day 1      | 128.9 (± 333.85)  | 94.0 (± 180.80)   |  |  |
| VEGF: Cycle 3 Day 1      | 97.7 (± 162.39)   | 66.0 (± 124.58)   |  |  |
| VEGF: Cycle 4 Day 1      | 113.4 (± 231.19)  | 76.1 (± 111.20)   |  |  |
| VEGF: Cycle 5 Day 1      | 132.4 (± 249.59)  | 116.2 (± 215.57)  |  |  |
| VEGF: Cycle 6 Day 1      | 113.1 (± 219.36)  | 130.9 (± 341.12)  |  |  |
| VEGF: Cycle 7 Day 1      | 133.1 (± 383.43)  | 96.9 (± 173.77)   |  |  |
| VEGF: Cycle 8 Day 1      | 148.7 (± 349.58)  | 181.1 (± 399.67)  |  |  |
| VEGF: Cycle 9 Day 1      | 129.6 (± 215.05)  | 135.6 (± 267.61)  |  |  |
| VEGF: Off-Treatment      | 127.1 (± 266.64)  | 147.8 (± 304.31)  |  |  |

## **Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All treatment-emergent adverse events were collected from first dose of study drug (Baseline) up to 30 days after last dose of study drug (approximately up to 8 years)

Adverse event reporting additional description:

The safety analysis set included all subjects who received at least 1 dose of study drug. Total number of Deaths (all-causes) was reported for all subjects randomized that is Total number of subjects exposed for Lenvatinib were 478 and for Sorafenib were 476.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Sorafenib |
|-----------------------|-----------|

Reporting group description:

Subjects received sorafenib 400 mg tablets, orally, twice daily in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

|                       |            |
|-----------------------|------------|
| Reporting group title | Lenvatinib |
|-----------------------|------------|

Reporting group description:

Subjects received lenvatinib capsules 12 mg based on the subject's body weight  $\geq 60$  kg or 8 mg based on the subject's body weight  $< 60$  kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

| Serious adverse events                                              | Sorafenib          | Lenvatinib         |  |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed                                         | 149 / 475 (31.37%) | 209 / 476 (43.91%) |  |
| number of deaths (all causes)                                       | 402                | 415                |  |
| number of deaths resulting from adverse events                      |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Malignant neoplasm progression                                      |                    |                    |  |
| subjects affected / exposed                                         | 14 / 475 (2.95%)   | 11 / 476 (2.31%)   |  |
| occurrences causally related to treatment / all                     | 0 / 14             | 0 / 12             |  |
| deaths causally related to treatment / all                          | 0 / 14             | 0 / 11             |  |
| Cancer pain                                                         |                    |                    |  |
| subjects affected / exposed                                         | 0 / 475 (0.00%)    | 4 / 476 (0.84%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 4              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Tumour haemorrhage                                                  |                    |                    |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 475 (0.63%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Liver carcinoma ruptured                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Metastases to central nervous system            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Metastases to spine                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infected neoplasm                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial tumour haemorrhage                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningioma                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to bone                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cell carcinoma                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour necrosis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour pain                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm malignant                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant ascites                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant pleural effusion                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Plasma cell myeloma                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mantle cell lymphoma                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to adrenals                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic dissection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shock                                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis superficial                    |                 |                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Pyrexia                                              |                 |                 |  |
| subjects affected / exposed                          | 5 / 475 (1.05%) | 7 / 476 (1.47%) |  |
| occurrences causally related to treatment / all      | 4 / 6           | 4 / 8           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 1 / 475 (0.21%) | 7 / 476 (1.47%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 4 / 7           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 3 / 475 (0.63%) | 5 / 476 (1.05%) |  |
| occurrences causally related to treatment / all      | 0 / 4           | 1 / 5           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 2           |  |
| Oedema peripheral                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 475 (0.21%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Fatigue                                              |                 |                 |  |
| subjects affected / exposed                          | 2 / 475 (0.42%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 2           |  |
| Death                                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 2           |  |
| Generalised oedema                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral swelling                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organ failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 1           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Pelvic pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 5 / 476 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 4 / 476 (0.84%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 475 (0.63%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 3 / 4           |  |
| deaths causally related to treatment / all      | 1 / 3           | 2 / 3           |  |
| Hepatopulmonary syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Hiccups                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrotising bronchiolitis                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiogenic pulmonary oedema                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oropharyngeal pain                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary infarction                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumothorax                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Major depression                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 7 / 476 (1.47%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 3 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase                      |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| increased                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood pressure decreased                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium test positive                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 5 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Accidental overdose                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intentional overdose                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foreign body                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax traumatic                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Traumatic haematoma                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 4 / 476 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 4 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiopulmonary failure                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Heart valve stenosis                            |                 |                 |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac failure                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Coronary artery disease                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| Nervous system disorders                        |                 |                  |  |
| Hepatic encephalopathy                          |                 |                  |  |
| subjects affected / exposed                     | 3 / 475 (0.63%) | 21 / 476 (4.41%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 13 / 35          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            |  |
| Cerebral haemorrhage                            |                 |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 3 / 476 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 5 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 3 / 3            |  |
| Coma hepatic                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 3 / 476 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            |  |
| Cerebral infarction                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cerebrovascular accident                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 2            |  |
| Headache                                        |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord compression                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diplegia                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disturbance in attention                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Facial paralysis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paralysis recurrent laryngeal nerve             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Posterior reversible encephalopathy syndrome    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Basal ganglia haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombotic cerebral infarction                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 475 (1.26%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 7 / 12          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone marrow failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 5 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated intravascular coagulation          |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Anaemia vitamin B12 deficiency                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Hypoacusis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertigo                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Gastrointestinal disorders                      |                  |                  |  |
| Ascites                                         |                  |                  |  |
| subjects affected / exposed                     | 12 / 475 (2.53%) | 12 / 476 (2.52%) |  |
| occurrences causally related to treatment / all | 5 / 15           | 8 / 15           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 475 (0.42%)  | 8 / 476 (1.68%)  |  |
| occurrences causally related to treatment / all | 2 / 2            | 7 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal varices haemorrhage                 |                  |                  |  |
| subjects affected / exposed                     | 5 / 475 (1.05%)  | 7 / 476 (1.47%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 3 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 11 / 475 (2.32%) | 6 / 476 (1.26%)  |  |
| occurrences causally related to treatment / all | 1 / 11           | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%)  | 6 / 476 (1.26%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 2 / 475 (0.42%)  | 6 / 476 (1.26%)  |  |
| occurrences causally related to treatment / all | 2 / 5            | 4 / 7            |  |
| deaths causally related to treatment / all      | 0 / 2            | 1 / 2            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%)  | 3 / 476 (0.63%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea                                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%)  | 3 / 476 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal distension                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain lower                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspepsia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 475 (0.63%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal haemorrhage                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Varices oesophageal                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Food poisoning                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric perforation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haematochezia                                   |                 |                  |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haemorrhoids                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                 |                  |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Peritoneal haemorrhage                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hepatobiliary disorders                         |                 |                  |  |
| Hepatic failure                                 |                 |                  |  |
| subjects affected / exposed                     | 8 / 475 (1.68%) | 14 / 476 (2.94%) |  |
| occurrences causally related to treatment / all | 3 / 11          | 8 / 22           |  |
| deaths causally related to treatment / all      | 0 / 2           | 3 / 10           |  |
| Jaundice cholestatic                            |                 |                  |  |
| subjects affected / exposed                     | 4 / 475 (0.84%) | 7 / 476 (1.47%)  |  |
| occurrences causally related to treatment / all | 0 / 4           | 2 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Portal vein thrombosis                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 4 / 476 (0.84%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            |  |
| Cholangitis                                     |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 475 (0.42%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hepatic cirrhosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bile duct obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bile duct stone                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute hepatic failure                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Biliary dilatation                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic hepatic failure                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Haemobilia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 475 (1.05%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 5 / 6           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hepatorenal syndrome                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic pain                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrocholecystis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver injury                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 475 (0.84%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Intertrigo                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug eruption                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seborrhoeic dermatitis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erythema multiforme                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psoriasis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Palmar-plantar erythrodysaesthesia syndrome     |                 |                 |  |
| subjects affected / exposed                     | 3 / 475 (0.63%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Proteinuria                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 4 / 476 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 3 / 476 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| IgA nephropathy                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 475 (1.05%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 5 / 475 (1.05%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal column stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal osteoarthritis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 475 (1.05%) | 5 / 476 (1.05%) |  |
| occurrences causally related to treatment / all | 1 / 7           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 3 / 475 (0.63%) | 7 / 476 (1.47%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 2 / 11          |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 5           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver abscess                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis bacterial                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendiceal abscess                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biliary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dengue fever                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastrointestinal viral infection                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Groin abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infectious pleural effusion                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perihepatic abscess                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periodontitis                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural infection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative abscess                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Salmonellosis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Scrotal infection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection enterococcal            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute sinusitis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspergillus infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic foot infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ophthalmic herpes simplex                       |                 |                 |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Perineal abscess                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia escherichia                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Upper respiratory tract infection               |                 |                  |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Metabolism and nutrition disorders              |                 |                  |  |
| Decreased appetite                              |                 |                  |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 11 / 476 (2.31%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 8 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hyponatraemia                                   |                 |                  |  |
| subjects affected / exposed                     | 2 / 475 (0.42%) | 3 / 476 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dehydration                                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hyperkalaemia                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 2 / 476 (0.42%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cachexia                                        |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoalbuminaemia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoproteinaemia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 475 (0.21%) | 0 / 476 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomagnesaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 475 (0.00%) | 1 / 476 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Sorafenib          | Lenvatinib         |  |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 469 / 475 (98.74%) | 469 / 476 (98.53%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypertension                                          |                    |                    |  |
| subjects affected / exposed                           | 147 / 475 (30.95%) | 200 / 476 (42.02%) |  |
| occurrences (all)                                     | 269                | 419                |  |
| General disorders and administration site conditions  |                    |                    |  |
| Asthenia                                              |                    |                    |  |
| subjects affected / exposed                           | 48 / 475 (10.11%)  | 53 / 476 (11.13%)  |  |
| occurrences (all)                                     | 84                 | 122                |  |
| Fatigue                                               |                    |                    |  |
| subjects affected / exposed                           | 120 / 475 (25.26%) | 141 / 476 (29.62%) |  |
| occurrences (all)                                     | 170                | 226                |  |
| Oedema peripheral                                     |                    |                    |  |
| subjects affected / exposed                           | 33 / 475 (6.95%)   | 67 / 476 (14.08%)  |  |
| occurrences (all)                                     | 45                 | 107                |  |
| Pyrexia                                               |                    |                    |  |
| subjects affected / exposed                           | 61 / 475 (12.84%)  | 63 / 476 (13.24%)  |  |
| occurrences (all)                                     | 74                 | 79                 |  |
| Respiratory, thoracic and mediastinal disorders       |                    |                    |  |
| Cough                                                 |                    |                    |  |
| subjects affected / exposed                           | 37 / 475 (7.79%)   | 45 / 476 (9.45%)   |  |
| occurrences (all)                                     | 46                 | 54                 |  |
| Dysphonia                                             |                    |                    |  |
| subjects affected / exposed                           | 57 / 475 (12.00%)  | 113 / 476 (23.74%) |  |
| occurrences (all)                                     | 69                 | 134                |  |
| Epistaxis                                             |                    |                    |  |
| subjects affected / exposed                           | 15 / 475 (3.16%)   | 35 / 476 (7.35%)   |  |
| occurrences (all)                                     | 17                 | 35                 |  |
| Dyspnoea                                              |                    |                    |  |
| subjects affected / exposed                           | 17 / 475 (3.58%)   | 31 / 476 (6.51%)   |  |
| occurrences (all)                                     | 19                 | 39                 |  |
| Psychiatric disorders                                 |                    |                    |  |



|                                                                                          |                           |                           |  |
|------------------------------------------------------------------------------------------|---------------------------|---------------------------|--|
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 28 / 475 (5.89%)<br>34    | 33 / 476 (6.93%)<br>38    |  |
| Investigations                                                                           |                           |                           |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 51 / 475 (10.74%)<br>108  | 53 / 476 (11.13%)<br>86   |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 29 / 475 (6.11%)<br>40    | 32 / 476 (6.72%)<br>59    |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 80 / 475 (16.84%)<br>173  | 64 / 476 (13.45%)<br>128  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 63 / 475 (13.26%)<br>128  | 67 / 476 (14.08%)<br>141  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)           | 13 / 475 (2.74%)<br>21    | 41 / 476 (8.61%)<br>101   |  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 27 / 475 (5.68%)<br>41    | 37 / 476 (7.77%)<br>60    |  |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)       | 24 / 475 (5.05%)<br>62    | 33 / 476 (6.93%)<br>59    |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)             | 59 / 475 (12.42%)<br>127  | 87 / 476 (18.28%)<br>260  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 108 / 475 (22.74%)<br>182 | 149 / 476 (31.30%)<br>290 |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)     | 25 / 475 (5.26%)<br>55    | 47 / 476 (9.87%)<br>115   |  |
| Nervous system disorders                                                                 |                           |                           |  |

|                                      |                    |                    |  |
|--------------------------------------|--------------------|--------------------|--|
| Headache                             |                    |                    |  |
| subjects affected / exposed          | 39 / 475 (8.21%)   | 45 / 476 (9.45%)   |  |
| occurrences (all)                    | 48                 | 57                 |  |
| Dizziness                            |                    |                    |  |
| subjects affected / exposed          | 16 / 475 (3.37%)   | 29 / 476 (6.09%)   |  |
| occurrences (all)                    | 22                 | 33                 |  |
| Hepatic encephalopathy               |                    |                    |  |
| subjects affected / exposed          | 6 / 475 (1.26%)    | 24 / 476 (5.04%)   |  |
| occurrences (all)                    | 6                  | 37                 |  |
| Blood and lymphatic system disorders |                    |                    |  |
| Anaemia                              |                    |                    |  |
| subjects affected / exposed          | 43 / 475 (9.05%)   | 35 / 476 (7.35%)   |  |
| occurrences (all)                    | 104                | 55                 |  |
| Thrombocytopenia                     |                    |                    |  |
| subjects affected / exposed          | 28 / 475 (5.89%)   | 33 / 476 (6.93%)   |  |
| occurrences (all)                    | 90                 | 81                 |  |
| Gastrointestinal disorders           |                    |                    |  |
| Abdominal distension                 |                    |                    |  |
| subjects affected / exposed          | 24 / 475 (5.05%)   | 39 / 476 (8.19%)   |  |
| occurrences (all)                    | 27                 | 57                 |  |
| Abdominal pain                       |                    |                    |  |
| subjects affected / exposed          | 83 / 475 (17.47%)  | 82 / 476 (17.23%)  |  |
| occurrences (all)                    | 111                | 136                |  |
| Abdominal pain upper                 |                    |                    |  |
| subjects affected / exposed          | 41 / 475 (8.63%)   | 58 / 476 (12.18%)  |  |
| occurrences (all)                    | 59                 | 82                 |  |
| Ascites                              |                    |                    |  |
| subjects affected / exposed          | 39 / 475 (8.21%)   | 63 / 476 (13.24%)  |  |
| occurrences (all)                    | 54                 | 82                 |  |
| Constipation                         |                    |                    |  |
| subjects affected / exposed          | 52 / 475 (10.95%)  | 76 / 476 (15.97%)  |  |
| occurrences (all)                    | 62                 | 95                 |  |
| Diarrhoea                            |                    |                    |  |
| subjects affected / exposed          | 223 / 475 (46.95%) | 186 / 476 (39.08%) |  |
| occurrences (all)                    | 448                | 406                |  |
| Dyspepsia                            |                    |                    |  |

|                                            |                    |                    |  |
|--------------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed                | 18 / 475 (3.79%)   | 31 / 476 (6.51%)   |  |
| occurrences (all)                          | 20                 | 40                 |  |
| Stomatitis                                 |                    |                    |  |
| subjects affected / exposed                | 56 / 475 (11.79%)  | 45 / 476 (9.45%)   |  |
| occurrences (all)                          | 76                 | 67                 |  |
| Nausea                                     |                    |                    |  |
| subjects affected / exposed                | 71 / 475 (14.95%)  | 90 / 476 (18.91%)  |  |
| occurrences (all)                          | 94                 | 131                |  |
| Vomiting                                   |                    |                    |  |
| subjects affected / exposed                | 37 / 475 (7.79%)   | 75 / 476 (15.76%)  |  |
| occurrences (all)                          | 65                 | 110                |  |
| Dry mouth                                  |                    |                    |  |
| subjects affected / exposed                | 8 / 475 (1.68%)    | 32 / 476 (6.72%)   |  |
| occurrences (all)                          | 8                  | 38                 |  |
| Skin and subcutaneous tissue disorders     |                    |                    |  |
| Alopecia                                   |                    |                    |  |
| subjects affected / exposed                | 120 / 475 (25.26%) | 15 / 476 (3.15%)   |  |
| occurrences (all)                          | 140                | 16                 |  |
| Palmar-plantar erythrodysesthesia syndrome |                    |                    |  |
| subjects affected / exposed                | 246 / 475 (51.79%) | 128 / 476 (26.89%) |  |
| occurrences (all)                          | 614                | 236                |  |
| Pruritus                                   |                    |                    |  |
| subjects affected / exposed                | 35 / 475 (7.37%)   | 34 / 476 (7.14%)   |  |
| occurrences (all)                          | 46                 | 41                 |  |
| Rash                                       |                    |                    |  |
| subjects affected / exposed                | 77 / 475 (16.21%)  | 46 / 476 (9.66%)   |  |
| occurrences (all)                          | 105                | 59                 |  |
| Renal and urinary disorders                |                    |                    |  |
| Proteinuria                                |                    |                    |  |
| subjects affected / exposed                | 55 / 475 (11.58%)  | 117 / 476 (24.58%) |  |
| occurrences (all)                          | 125                | 363                |  |
| Haematuria                                 |                    |                    |  |
| subjects affected / exposed                | 9 / 475 (1.89%)    | 25 / 476 (5.25%)   |  |
| occurrences (all)                          | 11                 | 34                 |  |
| Endocrine disorders                        |                    |                    |  |

|                                                                                       |                           |                           |  |
|---------------------------------------------------------------------------------------|---------------------------|---------------------------|--|
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 475 (1.68%)<br>9      | 81 / 476 (17.02%)<br>104  |  |
| Musculoskeletal and connective tissue disorders                                       |                           |                           |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 20 / 475 (4.21%)<br>31    | 42 / 476 (8.82%)<br>52    |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 28 / 475 (5.89%)<br>30    | 48 / 476 (10.08%)<br>55   |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)              | 25 / 475 (5.26%)<br>30    | 47 / 476 (9.87%)<br>56    |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 18 / 475 (3.79%)<br>32    | 38 / 476 (7.98%)<br>59    |  |
| Infections and infestations                                                           |                           |                           |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 25 / 475 (5.26%)<br>33    | 23 / 476 (4.83%)<br>26    |  |
| Metabolism and nutrition disorders                                                    |                           |                           |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                  | 38 / 475 (8.00%)<br>56    | 43 / 476 (9.03%)<br>88    |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 126 / 475 (26.53%)<br>165 | 162 / 476 (34.03%)<br>269 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 26 / 475 (5.47%)<br>52    | 9 / 476 (1.89%)<br>14     |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 January 2014 | Protocol Amendment 1: Revisions included changes to the inclusion/exclusion criteria and clarification of study conduct/procedures based on feedback from the investigators, addition of safety monitoring procedures as a result of the EU Voluntary Harmonisation Procedure (VHP) for protocol review, and updating of the instruments used to collect HRQoL.                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 09 April 2014   | Protocol Amendment 2: As required by the Japanese regulatory authority (Pharmaceuticals and Medical Devices Agency), clarified that although progression of HCC was not to be reported as a TEAE, if the progression led to an untoward medical occurrence, this untoward medical occurrence was to be reported as a TEAE. Revision of Exclusion Criteria #10 to clarify that subjects who required active interventional treatment of gastric or esophageal varices within 28 days prior to randomization were to be excluded. As required by the French Health authority, clarified toxicity management for sorafenib-treated subjects with QTc prolongation ( $\geq 501$ msec) and advised caution when using medicines that are known to prolong the QTc interval when used concomitantly with sorafenib. |
| 16 January 2015 | Protocol Amendment 3: As requested during the EU VHP review, information on the occurrence, diagnosis, and management of PRES in lenvatinib-treated subjects was added. As requested by the French Health Authority, since the occurrence of PRES was added to the lenvatinib Investigator's Brochure as an "expected" adverse event, any further reports of PRES were no longer subject to expedited reporting to regulatory authorities.                                                                                                                                                                                                                                                                                                                                                                    |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported