



## Clinical trial results:

### A Randomized, Double-Blind, Phase III Study of the Efficacy and Safety of Gemcitabine in Combination With TH-302 Compared With Gemcitabine in Combination With Placebo in Previously Untreated Subjects With Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2012-002957-42                      |
| Trial protocol           | BE GB CZ DE HU ES SK IT PL FI NL AT |
| Global end of trial date | 04 May 2016                         |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 July 2018 |
| First version publication date | 11 July 2018 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | EMR200592-001 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01746979 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Molecular Templates (formerly Threshold Pharmaceuticals)                                     |
| Sponsor organisation address | 9301 Amberglen Blvd, Suite 100, Austin, United States, TX 78729                              |
| Public contact               | Kristina Dabovic, PharmD, Molecular Templates, +1 (862) 204-7184, kristina.dabovic@mttem.com |
| Scientific contact           | Nenad Sarapa, MD, Molecular Templates, +1 (973) 796-6104, nenad.sarapa@mttem.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                       | 04 May 2016 |
| Is this the analysis of the primary completion data? | No          |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 04 May 2016 |
| Was the trial ended prematurely? | No          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate efficacy, as measured by overall survival (OS), of gemcitabine in combination with TH-302 compared to gemcitabine in combination with placebo in subjects with previously untreated locally advanced unresectable or metastatic pancreatic adenocarcinoma.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 24 January 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 | Brazil: 5              |
| Country: Number of subjects enrolled | Canada: 15             |
| Country: Number of subjects enrolled | Israel: 21             |
| Country: Number of subjects enrolled | Japan: 116             |
| Country: Number of subjects enrolled | Korea, Republic of: 7  |
| Country: Number of subjects enrolled | Romania: 12            |
| Country: Number of subjects enrolled | Russian Federation: 54 |
| Country: Number of subjects enrolled | United States: 81      |
| Country: Number of subjects enrolled | Netherlands: 4         |
| Country: Number of subjects enrolled | Poland: 23             |
| Country: Number of subjects enrolled | Slovakia: 6            |
| Country: Number of subjects enrolled | Spain: 45              |
| Country: Number of subjects enrolled | United Kingdom: 39     |
| Country: Number of subjects enrolled | Austria: 6             |
| Country: Number of subjects enrolled | Belgium: 49            |
| Country: Number of subjects enrolled | Czech Republic: 35     |
| Country: Number of subjects enrolled | Finland: 13            |
| Country: Number of subjects enrolled | France: 58             |
| Country: Number of subjects enrolled | Germany: 24            |

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Hungary: 40   |
| Country: Number of subjects enrolled | Italy: 17     |
| Country: Number of subjects enrolled | Argentina: 4  |
| Country: Number of subjects enrolled | Australia: 19 |
| Worldwide total number of subjects   | 693           |
| EEA total number of subjects         | 371           |

Notes:

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### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 325 |
| From 65 to 84 years                       | 367 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 969 subjects were screened, out of which 693 subjects were randomized in the study.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Period (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Double blind                    |
| Roles blinded                | Subject, Investigator           |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Gemcitabine Plus TH-302 |
|------------------|-------------------------|

Arm description:

TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m<sup>2</sup>) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | TH-302            |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

TH-302 was administered at a dose of 340 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Gemcitabine     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Gemcitabine Plus Placebo |
|------------------|--------------------------|

Arm description:

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Gemcitabine     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | Placebo (5 percent dextrose - D5W) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Infusion                           |
| Routes of administration               | Intravenous use                    |

Dosage and administration details:

TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

| <b>Number of subjects in period 1</b> | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo |
|---------------------------------------|-------------------------|--------------------------|
| Started                               | 346                     | 347                      |
| Completed                             | 0                       | 0                        |
| Not completed                         | 346                     | 347                      |
| Discontinued                          | 346                     | 347                      |

## Baseline characteristics

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Gemcitabine Plus TH-302 |
|-----------------------|-------------------------|

Reporting group description:

TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m<sup>2</sup>) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Gemcitabine Plus Placebo |
|-----------------------|--------------------------|

Reporting group description:

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

| Reporting group values             | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo | Total |
|------------------------------------|-------------------------|--------------------------|-------|
| Number of subjects                 | 346                     | 347                      | 693   |
| Age categorical<br>Units: Subjects |                         |                          |       |

|   |              |                |     |
|---|--------------|----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 65<br>± 9.70 | 63.8<br>± 9.82 | -   |
| Gender categorical<br>Units: Subjects                                   |              |                |     |
| Female  | 155          | 168            | 323 |
| Male  | 191          | 179            | 370 |

## End points

### End points reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Gemcitabine Plus TH-302  |
| Reporting group description:<br>TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m <sup>2</sup> ) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.<br>Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m <sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal. |                          |
| Reporting group title  | Gemcitabine Plus Placebo |
| Reporting group description:<br>Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m <sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.<br>Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.    |                          |

### Primary: Overall Survival

|   |                  |
|---|------------------|
| End point title   | Overall Survival |
| End point description:<br>Overall survival is defined as time from randomization to death or last day known to be alive.                    |                  |
| End point type  | Primary          |
| End point timeframe:<br>From date of randomization until date of death from any cause or last day known to be alive, assessed up to 2 years |                  |

| End point values                 | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo |  |  |
|----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed      | 346                     | 347                      |  |  |
| Units: Months                    |                         |                          |  |  |
| median (confidence interval 95%) | 8.9 (7.6 to 9.9)        | 7.6 (6.7 to 8.3)         |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Statistical analysis of Overall Survival           |
| Comparison groups                       | Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo |
| Number of subjects included in analysis | 693  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.0588   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)                                  |
| Point estimate                          | 0.844  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.708   |
| upper limit         | 1.006   |

## Secondary: Progression Free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

Progression Free Survival is defined as the time from randomization to either first observation of progressive disease or occurrence of death. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

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

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 2 years

| End point values                 | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo |  |  |
|----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed      | 346                     | 347                      |  |  |
| Units: Months                    |                         |                          |  |  |
| median (confidence interval 95%) | 5.5 (4.8 to 5.6)        | 3.7 (3.6 to 3.8)         |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Statistical Analysis of Progression-free Survival  |
| Comparison groups                       | Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo |
| Number of subjects included in analysis | 693  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.0015   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)                                  |
| Point estimate                          | 0.747  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.623  |
| upper limit                             | 0.895  |

## Secondary: Objective Response Rate



|  |                         |
|--|-------------------------|
| End point title  | Objective Response Rate |
| End point description:<br>Objective response rate defined as the percentage of subjects having achieved complete response (CR: Disappearance of all target lesions) or partial response (PR: At least a 30 percent decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) as the best overall response according to local unconfirmed radiological assessments from randomization until the end of study treatment. |                         |
| End point type   | Secondary               |
| End point timeframe:<br>From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 2 years  |                         |

| End point values                 | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo |  |  |
|----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed      | 346                     | 347                      |  |  |
| Units: Percentage of Subjects    |                         |                          |  |  |
| number (confidence interval 95%) | 20.5 (16.4 to 25.2)     | 17.3 (13.5 to 21.7)      |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Statistical analysis of Objective Response Rate    |
| Comparison groups                       | Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo |
| Number of subjects included in analysis | 693  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.2757   |
| Method                                  | Cochran-Mantel-Haenszel                            |
| Parameter estimate                      | Odds ratio (OR)                                    |
| Point estimate                          | 1.26   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.84   |
| upper limit                             | 1.89   |

## Secondary: Disease Control Rate

|  |                      |
|--|----------------------|
| End point title  | Disease Control Rate |
| End point description:<br>Disease control rate defined as the percentage of subjects having achieved CR, PR or stable disease (SD) as the best overall response according to local radiological assessments from randomization until the end of study treatment. |                      |
| End point type   | Secondary            |
| End point timeframe:<br>From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 2 years  |                      |

| <b>End point values</b>          | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo |  |  |
|----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed      | 346                     | 347                      |  |  |
| Units: Percentage of Subjects    |                         |                          |  |  |
| number (confidence interval 95%) | 69.1 (63.9 to 73.9)     | 63.1 (57.8 to 68.2)      |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical analysis of Disease Control Rate       |
|---|--|
| Comparison groups                       | Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo |
| Number of subjects included in analysis | 693  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.085  |
| Method                                  | Cochran-Mantel-Haenszel                            |
| Parameter estimate                      | Odds ratio (OR)                                    |
| Point estimate                          | 1.32   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.95   |
| upper limit                             | 1.83   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 2 years

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Gemcitabine Plus TH-302 |
|-----------------------|-------------------------|

Reporting group description:

TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m<sup>2</sup>) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Gemcitabine Plus Placebo |
|-----------------------|--------------------------|

Reporting group description:

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

| Serious adverse events  | Gemcitabine Plus TH-302 | Gemcitabine Plus Placebo |  |
|---|-------------------------|--------------------------|--|
| Total subjects affected by serious adverse events                   |                         |                          |  |
| subjects affected / exposed   | 183 / 338 (54.14%)      | 177 / 341 (51.91%)       |  |
| number of deaths (all causes)                                       | 241                     | 260                      |  |
| number of deaths resulting from adverse events                      |                         |                          |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                          |  |
| Cancer pain   |                         |                          |  |
| subjects affected / exposed   | 2 / 338 (0.59%)         | 2 / 341 (0.59%)          |  |
| occurrences causally related to treatment / all                     | 0 / 2                   | 0 / 3                    |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                    |  |
| Malignant ascites   |                         |                          |  |
| subjects affected / exposed   | 1 / 338 (0.30%)         | 1 / 341 (0.29%)          |  |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 1                    |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                    |  |
| Paraneoplastic syndrome   |                         |                          |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic dissection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial occlusive disease                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Arterial thrombosis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Axillary vein thrombosis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 7 / 338 (2.07%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 1 / 7           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolism  |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hypertension                                    |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Phlebitis  |                 |                 |  |
| subjects affected / exposed                          | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Thrombophlebitis                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venous thrombosis                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venous thrombosis limb                               |                 |                 |  |
| subjects affected / exposed                          | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 338 (1.18%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Chills  |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 2 / 341 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device malfunction                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device occlusion                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 338 (0.89%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Disease progression                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 338 (1.18%)  | 2 / 341 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 2            |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                     | 2 / 338 (0.59%)  | 3 / 341 (0.88%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |
| subjects affected / exposed                     | 11 / 338 (3.25%) | 14 / 341 (4.11%) |  |
| occurrences causally related to treatment / all | 1 / 12           | 1 / 15           |  |
| deaths causally related to treatment / all      | 1 / 7            | 1 / 9            |  |
| Generalised oedema                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infusion site extravasation                     |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injection site extravasation                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Local swelling                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise   |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain  |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 14 / 338 (4.14%) | 11 / 341 (3.23%) |  |
| occurrences causally related to treatment / all | 3 / 15           | 5 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stent malfunction                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sudden death                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Immune system disorders                         |                  |                  |  |
| Anaphylactic reaction                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug hypersensitivity                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypersensitivity                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute interstitial pneumonitis                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute pulmonary oedema                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea exertional                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (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                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hiccups   |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary embolism                              |                  |                  |  |
| subjects affected / exposed                     | 11 / 338 (3.25%) | 10 / 341 (2.93%) |  |
| occurrences causally related to treatment / all | 1 / 11           | 2 / 10           |  |
| deaths causally related to treatment / all      | 1 / 1            | 1 / 1            |  |
| Respiratory failure                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Anxiety   |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| 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                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 2 / 341 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental status changes                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 338 (0.59%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide attempt                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood alkaline phosphatase increased            |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood glucose fluctuation                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| C-reactive protein increased                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| subjects affected / exposed                     | 4 / 338 (1.18%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical condition abnormal             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver function test abnormal                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 8 / 338 (2.37%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 6 / 8           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Accidental overdose                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chemical peritonitis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion related reaction                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural bile leak                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prescribed overdose                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic haemothorax                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Pyloric stenosis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Aortic valve disease                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial tachycardia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Amnesia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Balance disorder                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral artery stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Coma  |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemianopia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (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 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Spinal cord compression                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 16 / 338 (4.73%) | 15 / 341 (4.40%) |  |
| occurrences causally related to treatment / all | 8 / 18           | 4 / 18           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone marrow failure                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (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                     | 6 / 338 (1.78%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 6 / 7            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukocytosis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukopenia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 9 / 338 (2.66%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 12 / 13          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 338 (0.59%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Splenic infarction                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Splenic vein thrombosis                         |                  |                  |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombocytopenia                                |                  |                 |  |
| subjects affected / exposed                     | 19 / 338 (5.62%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 17 / 25          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |
| Macular hole                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Abdominal distension                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain                                  |                  |                 |  |
| subjects affected / exposed                     | 10 / 338 (2.96%) | 7 / 341 (2.05%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain upper                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ascites   |                  |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%)  | 5 / 341 (1.47%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Colitis ischaemic                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Constipation                                    |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 8 / 338 (2.37%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 9 / 11          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal obstruction                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal perforation                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer haemorrhage                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric perforation                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer perforation                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal inflammation                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal perforation                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired gastric emptying                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal perforation                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Intra-abdominal haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstruction gastric                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedematous pancreatitis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Oesophageal ulcer                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal varices haemorrhage                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proctalgia                                      |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Small intestinal obstruction                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 2 / 341 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Stomatitis                                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Subileus  |                 |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 3 / 341 (0.88%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            |  |
| Upper gastrointestinal haemorrhage              |                 |                  |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 2 / 341 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Vomiting  |                 |                  |  |
| subjects affected / exposed                     | 7 / 338 (2.07%) | 13 / 341 (3.81%) |  |
| occurrences causally related to treatment / all | 1 / 8           | 4 / 13           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hepatobiliary disorders                         |                 |                  |  |
| Bile duct obstruction                           |                 |                  |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 6 / 341 (1.76%)  |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bile duct stenosis                              |                 |                  |  |
| subjects affected / exposed                     | 5 / 338 (1.48%) | 5 / 341 (1.47%)  |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bile duct stone                                 |                 |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary dilatation                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 338 (0.59%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangiectasis acquired                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 0 / 341 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangiolitis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 338 (0.00%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |
| subjects affected / exposed                     | 12 / 338 (3.55%) | 15 / 341 (4.40%) |  |
| occurrences causally related to treatment / all | 1 / 12           | 3 / 21           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis acute                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 6 / 341 (1.76%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 338 (0.59%)  | 3 / 341 (0.88%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis acute                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 338 (0.30%)  | 1 / 341 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholestasis                                     |                  |                  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 338 (0.89%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gallbladder obstruction                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 1           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 4 / 338 (1.18%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatorenal failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice  |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Jaundice cholestatic                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 6 / 341 (1.76%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Portal hypertension                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Dermatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin maceration                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Yellow skin                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Dysuria   |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proteinuria                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract obstruction                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 338 (0.89%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gouty arthritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial prostatitis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biliary sepsis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Biliary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (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                     | 2 / 338 (0.59%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 3 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic gangrene                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| 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 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal infection                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis infectious                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| 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                     | 1 / 338 (0.30%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile infection                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fungal oesophagitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| 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 / 338 (0.30%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion site infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella bacteraemia                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella sepsis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (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 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningoencephalitis herpetic                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal candidiasis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oropharyngeal candidiasis                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic abscess                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Penile infection                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pharyngitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 8 / 338 (2.37%) | 9 / 341 (2.64%) |  |
| occurrences causally related to treatment / all | 2 / 8           | 1 / 11          |  |
| deaths causally related to treatment / all      | 1 / 1           | 1 / 3           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 5 / 338 (1.48%) | 5 / 341 (1.47%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Splenic abscess                                 |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 4 / 341 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vaginal infection                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (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              |                 |                 |  |
| Cachexia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 338 (0.59%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoalbuminaemia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypovolaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 338 (0.30%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic disorder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 338 (0.00%) | 1 / 341 (0.29%) |  |
| 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>                     | <b>Gemcitabine Plus<br/>TH-302</b> | <b>Gemcitabine Plus<br/>Placebo</b> |  |
|---|------------------------------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                    |                                     |  |
| subjects affected / exposed                           | 331 / 338 (97.93%)                 | 328 / 341 (96.19%)                  |  |
| Investigations  |                                    |                                     |  |
| Alanine aminotransferase increased                    |                                    |                                     |  |
| subjects affected / exposed                           | 34 / 338 (10.06%)                  | 30 / 341 (8.80%)                    |  |
| occurrences (all)                                     | 86                                 | 52                                  |  |
| Aspartate aminotransferase increased                  |                                    |                                     |  |
| subjects affected / exposed                           | 29 / 338 (8.58%)                   | 27 / 341 (7.92%)                    |  |
| occurrences (all)                                     | 71                                 | 44                                  |  |
| Blood alkaline phosphatase increased                  |                                    |                                     |  |
| subjects affected / exposed                           | 20 / 338 (5.92%)                   | 29 / 341 (8.50%)                    |  |
| occurrences (all)                                     | 34                                 | 41                                  |  |
| Blood bilirubin increased                             |                                    |                                     |  |
| subjects affected / exposed                           | 21 / 338 (6.21%)                   | 22 / 341 (6.45%)                    |  |
| occurrences (all)                                     | 39                                 | 36                                  |  |
| Neutrophil count decreased                            |                                    |                                     |  |
| subjects affected / exposed                           | 52 / 338 (15.38%)                  | 29 / 341 (8.50%)                    |  |
| occurrences (all)                                     | 301                                | 94                                  |  |
| Platelet count decreased                              |                                    |                                     |  |
| subjects affected / exposed                           | 100 / 338 (29.59%)                 | 44 / 341 (12.90%)                   |  |
| occurrences (all)                                     | 476                                | 122                                 |  |
| Weight decreased                                      |                                    |                                     |  |
| subjects affected / exposed                           | 31 / 338 (9.17%)                   | 34 / 341 (9.97%)                    |  |
| occurrences (all)                                     | 38                                 | 38                                  |  |
| White blood cell count decreased                      |                                    |                                     |  |
| subjects affected / exposed                           | 55 / 338 (16.27%)                  | 28 / 341 (8.21%)                    |  |
| occurrences (all)                                     | 263                                | 84                                  |  |
| Vascular disorders                                    |                                    |                                     |  |
| Hypertension  |                                    |                                     |  |
| subjects affected / exposed                           | 16 / 338 (4.73%)                   | 21 / 341 (6.16%)                    |  |
| occurrences (all)                                     | 30                                 | 28                                  |  |
| Nervous system disorders                              |                                    |                                     |  |

|   |                           |                           |  |
|---|---------------------------|---------------------------|--|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)         | 28 / 338 (8.28%)<br>38    | 24 / 341 (7.04%)<br>32    |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)         | 46 / 338 (13.61%)<br>57   | 33 / 341 (9.68%)<br>39    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)          | 23 / 338 (6.80%)<br>29    | 26 / 341 (7.62%)<br>33    |  |
| Blood and lymphatic system disorders                                  |                           |                           |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)           | 164 / 338 (48.52%)<br>582 | 108 / 341 (31.67%)<br>254 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)        | 47 / 338 (13.91%)<br>198  | 29 / 341 (8.50%)<br>47    |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)       | 140 / 338 (41.42%)<br>546 | 94 / 341 (27.57%)<br>248  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)  | 158 / 338 (46.75%)<br>772 | 61 / 341 (17.89%)<br>151  |  |
| General disorders and administration<br>site conditions               |                           |                           |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)          | 81 / 338 (23.96%)<br>229  | 71 / 341 (20.82%)<br>165  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)           | 98 / 338 (28.99%)<br>234  | 106 / 341 (31.09%)<br>219 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 64 / 338 (18.93%)<br>87   | 72 / 341 (21.11%)<br>104  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)           | 64 / 338 (18.93%)<br>104  | 76 / 341 (22.29%)<br>147  |  |
| Gastrointestinal disorders  |                           |                           |  |

|  |                           |                           |  |
|--|---------------------------|---------------------------|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 65 / 338 (19.23%)<br>110  | 70 / 341 (20.53%)<br>149  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 44 / 338 (13.02%)<br>66   | 38 / 341 (11.14%)<br>58   |  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)              | 18 / 338 (5.33%)<br>18    | 29 / 341 (8.50%)<br>42    |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 104 / 338 (30.77%)<br>171 | 104 / 341 (30.50%)<br>146 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 112 / 338 (33.14%)<br>245 | 89 / 341 (26.10%)<br>181  |  |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)         | 39 / 338 (11.54%)<br>59   | 13 / 341 (3.81%)<br>15    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 168 / 338 (49.70%)<br>354 | 150 / 341 (43.99%)<br>320 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 86 / 338 (25.44%)<br>172  | 53 / 341 (15.54%)<br>78   |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 109 / 338 (32.25%)<br>243 | 109 / 341 (31.96%)<br>233 |  |
| Respiratory, thoracic and mediastinal disorders                          |                           |                           |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 28 / 338 (8.28%)<br>34    | 27 / 341 (7.92%)<br>30    |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)             | 44 / 338 (13.02%)<br>55   | 27 / 341 (7.92%)<br>44    |  |
| Skin and subcutaneous tissue disorders                                   |                           |                           |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Alopecia  |                   |                   |  |
| subjects affected / exposed                     | 68 / 338 (20.12%) | 23 / 341 (6.74%)  |  |
| occurrences (all)                               | 81                | 30                |  |
| Dry skin  |                   |                   |  |
| subjects affected / exposed                     | 22 / 338 (6.51%)  | 13 / 341 (3.81%)  |  |
| occurrences (all)                               | 30                | 13                |  |
| Erythema  |                   |                   |  |
| subjects affected / exposed                     | 25 / 338 (7.40%)  | 10 / 341 (2.93%)  |  |
| occurrences (all)                               | 32                | 12                |  |
| Pruritus  |                   |                   |  |
| subjects affected / exposed                     | 23 / 338 (6.80%)  | 25 / 341 (7.33%)  |  |
| occurrences (all)                               | 27                | 32                |  |
| Rash  |                   |                   |  |
| subjects affected / exposed                     | 63 / 338 (18.64%) | 46 / 341 (13.49%) |  |
| occurrences (all)                               | 104               | 65                |  |
| Skin hyperpigmentation                          |                   |                   |  |
| subjects affected / exposed                     | 44 / 338 (13.02%) | 3 / 341 (0.88%)   |  |
| occurrences (all)                               | 59                | 4                 |  |
| Psychiatric disorders                           |                   |                   |  |
| Insomnia  |                   |                   |  |
| subjects affected / exposed                     | 25 / 338 (7.40%)  | 33 / 341 (9.68%)  |  |
| occurrences (all)                               | 26                | 36                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 30 / 338 (8.88%)  | 45 / 341 (13.20%) |  |
| occurrences (all)                               | 35                | 58                |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 16 / 338 (4.73%)  | 18 / 341 (5.28%)  |  |
| occurrences (all)                               | 27                | 23                |  |
| Infections and infestations                     |                   |                   |  |
| Urinary tract infection                         |                   |                   |  |
| subjects affected / exposed                     | 30 / 338 (8.88%)  | 19 / 341 (5.57%)  |  |
| occurrences (all)                               | 44                | 36                |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Decreased appetite                              |                   |                   |  |

|                             |                    |                    |  |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 117 / 338 (34.62%) | 116 / 341 (34.02%) |  |
| occurrences (all)           | 205                | 184                |  |
| Hyperglycaemia              |                    |                    |  |
| subjects affected / exposed | 27 / 338 (7.99%)   | 23 / 341 (6.74%)   |  |
| occurrences (all)           | 44                 | 55                 |  |
| Hypokalaemia                |                    |                    |  |
| subjects affected / exposed | 22 / 338 (6.51%)   | 27 / 341 (7.92%)   |  |
| occurrences (all)           | 30                 | 36                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 27 June 2013 | <p>The changes made to Version 3.0 of the clinical trial protocol are as follows:</p> <ol style="list-style-type: none"><li>1. Clarification of the exclusion criteria with respect to alternative treatments (changes previously incorporated in Local Amendment 1 [9 April 2013], which was implemented in Belgium, Czech Republic, France, Germany, Hungary, Romania, Spain, and the United Kingdom).</li><li>2. Clarification of the investigator's obligations for emergency unblinding (changes previously incorporated in Local Amendment 1 [9 April 2013], which was implemented in Belgium, Czech Republic, France, Germany, Hungary, Romania, Spain, and the United Kingdom).</li><li>3. Minor modification to the "Numerical Rating Scale for Pain".</li><li>4. Addition of the trial acronym (MAESTRO: TH-302 in the treatment of Metastatic or locally Advanced unresectable pancreatic adenocarcinoma).</li><li>5. Correction of minor typographical errors in the document.</li></ol> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported