



## Clinical trial results:

**A prospective, phase III, controlled, multicentre, randomised clinical trial comparing combination gemcitabine and capecitabine therapy with concurrent and sequential chemoimmunotherapy using a telomerase vaccine in locally advanced and metastatic pancreatic cancer.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-000461-10 |
| Trial protocol           | GB             |
| Global end of trial date | 27 May 2012    |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 28 February 2019 |
| First version publication date | 28 February 2019 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | ISRCTN43482138 |
|-----------------------|----------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | The Royal Liverpool and Broadgreen University Hospitals NHS Trust   |
| Sponsor organisation address | Prescot Street, Liverpool, United Kingdom, L7 8XP   |
| Public contact               | Ms Charlotte Rawcliffe, Liverpool Cancer Trials Unit, University of Liverpool, 0151 794 8167, C.Rawcliffe@liverpool.ac.uk |
| Scientific contact           | Dr Victoria Shaw, GCLP Labs, University of Liverpool, 0151 706 4180, Victoria.Shaw@liverpool.ac.uk                        |

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                       | 25 April 2014 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 27 May 2011   |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 27 May 2012   |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the efficacy of GV1001 on length of survival when added concurrently or sequentially to the combination gemcitabine and capecitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma.

Protection of trial subjects:

Patients were asked to consent that data are recorded, collected, stored and processed and might be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

Data was processed in accordance with the general terms and conditions of the authorisation from the 'Information Commissioner's Office' to the LCTU, as required, according to national legislation implementing the Data Protection Directive; 95/46/EC.

Background therapy: -

Evidence for comparator:

For patients with locally advanced or metastatic pancreatic cancer, who wish to have, and are fit enough to benefit from, active treatment, chemotherapy with single agent gemcitabine has for several years been the standard of care. The recently reported results of the NCRI GEMCAP trial, a randomised comparison of gemcitabine versus the combination of gemcitabine and capecitabine, and associated meta-analysis demonstrated a statistically significant survival benefit for patients receiving the combined treatment with acceptable levels of toxicity. Therefore all subjects enrolled in this programme will receive the GEM-CAP combination chemotherapy.

The benefits of the combination, though real, are modest and continual efforts to improve our management of this disease are essential. Vaccination of pancreatic cancer patients with the Telomerase vaccine GV1001 has yielded promising results. It has been administered to over 100 subjects and has been well tolerated with no serious adverse events. The most commonly reported adverse events are injection site reactions, chills, nausea and dizziness of which the majority were of mild intensity. It is thus an attractive candidate therapy to add to gemcitabine and capecitabine in order to try and improve outcomes in this disease. This trial will not be placebo controlled as it is not felt to be acceptable to submit patients in the control arm to unnecessary injections.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 29 March 2007 |
| 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 | United Kingdom: 1062 |
| Worldwide total number of subjects   | 1062                 |
| EEA total number of subjects         | 1062                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 601 |
| From 65 to 84 years                       | 461 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

UK only. First patient, first visit (FPFV; date of randomisation): 29 Mar 2007 and date of close of recruitment of the study: 27 May 2011 (closed early based on the final interim analysis by the Independent Safety and Data Monitoring Committee (ISDMC) as the sequential immunotherapy arm appeared to be inferior), Quality of life, Pain assessment

### Pre-assignment

Screening details:

Histology/cytology, Informed consent, Inclusion criteria, Randomisation, Demography & medical history, Physical examination, Vital signs, ECOG Performance status, ECG, Haematology, Serum Chemistry, Genomic/Proteomic Sampling, Blood, Proteomic Sampling - Urine, CT scan (RECIST), CA19-9  
1573 patients screened, 108 patients declined, 402 ineligible

### Period 1

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

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| Arm title                    | Gemcitabine and Capecitabine Therapy |

Arm description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

|  |                                  |
|--|----------------------------------|
| Arm type                               | Active comparator                |
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             | Gemzar                           |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

1000mg/m<sup>2</sup> gemcitabine must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Capecitabine       |
| Investigational medicinal product code |                    |
| Other name                             | Xeloda             |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

830 mg/m<sup>2</sup> capecitabine must be administered orally morning and evening daily (total daily dose of 1660 mg/m<sup>2</sup>) unless toxicity occurs requiring dose adjustment

|  |                        |
|--|------------------------|
| Investigational medicinal product name | GV1001                 |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intradermal use        |

**Dosage and administration details:**

3.5 ml sterile single dosage

|                  |   |
|------------------|---|
| <b>Arm title</b> | Gemcitabine and Capecitabine then Sequential GV1001 Therapy |
|------------------|---|

**Arm description:**

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Capecitabine       |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

**Dosage and administration details:**

830 mg/m<sup>2</sup> capecitabine must be administered orally morning and evening daily (total daily dose of 1660 mg/m<sup>2</sup>) unless toxicity occurs requiring dose adjustment as described below.

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             | Gemzar                           |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

1000mg/m<sup>2</sup> gemcitabine must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment

|                  |   |
|------------------|---|
| <b>Arm title</b> | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|------------------|---|

**Arm description:**

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             | Gemzar                           |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

1000mg/m<sup>2</sup> gemcitabine must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Capecitabine       |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

830 mg/m<sup>2</sup> capecitabine must be administered orally morning and evening daily (total daily dose of 1660 mg/m<sup>2</sup>) unless toxicity occurs requiring dose adjustment as described below.

|  |                        |
|--|------------------------|
| Investigational medicinal product name | GV1001                 |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intradermal use        |

Dosage and administration details:

3.5 ml sterile single dosage

|  |  |
|--|--|
| Investigational medicinal product name | GM-CSF                                     |
| Investigational medicinal product code |  |
| Other name                             | Leukine                                    |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Subcutaneous use, Intravenous use          |

Dosage and administration details:

Sterile vials containing 250 g lyophilised Leukine

| Number of subjects in period 1 | Gemcitabine and<br>Capecitabine<br>Therapy | Gemcitabine and<br>Capecitabine then<br>Sequential GV1001<br>Therapy | Concurrent<br>Gemcitabine,<br>Capecitabine and<br>GV1001 Therapy |
|--------------------------------|--|--|--|
|                                |  |  |  |
| Started                        | 358  | 350  | 354  |
| Completed                      | 358  | 350  | 354  |

## Baseline characteristics

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Gemcitabine and Capecitabine Therapy |
|-----------------------|--------------------------------------|

#### Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

|                       |   |
|-----------------------|---|
| Reporting group title | Gemcitabine and Capecitabine then Sequential GV1001 Therapy |
|-----------------------|---|

#### Reporting group description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

|                       |   |
|-----------------------|---|
| Reporting group title | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|-----------------------|---|

#### Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

| Reporting group values  | Gemcitabine and Capecitabine Therapy | Gemcitabine and Capecitabine then Sequential GV1001 Therapy | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|---|--------------------------------------|---|---|
| Number of subjects  | 358                                  | 350   | 354   |
| Age categorical<br>Units: Subjects  |                                      |   |   |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                      |   |   |
| Age continuous<br>Units: years  |                                      |   |   |
| arithmetic mean   | 61.9                                 | 62.7  | 62.3  |
| standard deviation  | ± 9.6                                | ± 9.5   | ± 9.5   |

|                                       |     |     |     |
|---------------------------------------|-----|-----|-----|
| Gender categorical<br>Units: Subjects |     |     |     |
| Female                                | 209 | 203 | 196 |
| Male                                  | 149 | 147 | 158 |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 1062  |  |  |
| Age categorical<br>Units: Subjects                                      |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                   | 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)  | 0     |  |  |
| From 65-84 years  | 0     |  |  |
| 85 years and over   | 0     |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -     |  |  |
| Gender categorical<br>Units: Subjects                                   |       |  |  |
| Female  | 608   |  |  |
| Male  | 454   |  |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Full Analysis Set  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process.

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Safety Set      |
| Subject analysis set type  | Safety analysis |

Subject analysis set description:

All patients who received any trial treatment

|   |                   |            |  |
|---|-------------------|------------|--|
| <b>Reporting group values</b>                         | Full Analysis Set | Safety Set |  |
| Number of subjects                                    | 1062              | 1062       |  |
| Age categorical<br>Units: Subjects                    |                   |            |  |
| In utero  |                   |            |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |                   |            |  |
| Newborns (0-27 days)                                  |                   |            |  |
| Infants and toddlers (28 days-23 months)              |                   |            |  |
| Children (2-11 years)                                 |                   |            |  |



|                           |       |       |  |
|---------------------------|-------|-------|--|
| Adolescents (12-17 years) |       |       |  |
| Adults (18-64 years)      |       |       |  |
| From 65-84 years          |       |       |  |
| 85 years and over         |       |       |  |
| Age continuous            |       |       |  |
| Units: years              |       |       |  |
| arithmetic mean           | 62.3  | 62.3  |  |
| standard deviation        | ± 9.5 | ± 9.5 |  |
| Gender categorical        |       |       |  |
| Units: Subjects           |       |       |  |
| Female                    | 454   | 454   |  |
| Male                      | 608   | 608   |  |

## End points

### End points reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Gemcitabine and Capecitabine Therapy |
|-----------------------|--------------------------------------|

#### Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

|                       |   |
|-----------------------|---|
| Reporting group title | Gemcitabine and Capecitabine then Sequential GV1001 Therapy |
|-----------------------|---|

#### Reporting group description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

|                       |   |
|-----------------------|---|
| Reporting group title | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|-----------------------|---|

#### Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Full Analysis Set |
|----------------------------|-------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

#### Subject analysis set description:

In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process.

|                            |            |
|----------------------------|------------|
| Subject analysis set title | Safety Set |
|----------------------------|------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

#### Subject analysis set description:

All patients who received any trial treatment

### Primary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

#### End point description:

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

#### End point timeframe:

From randomisation until death by any cause

| <b>End point values</b>          | Gemcitabine and Capecitabine Therapy | Gemcitabine and Capecitabine then Sequential GV1001 Therapy | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |  |
|----------------------------------|--------------------------------------|---|---|--|
| Subject group type               | Reporting group                      | Reporting group   | Reporting group   |  |
| Number of subjects analysed      | 358                                  | 350   | 354   |  |
| Units: Subjects                  |                                      |   |   |  |
| median (confidence interval 95%) | 7.89 (7.07 to 8.85)                  | 6.94 (6.35 to 7.60)   | 8.36 (7.30 to 9.74)                                     |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Primary Efficacy Analysis Arm 1 Vs Arm 2 |
|-----------------------------------|--|
|-----------------------------------|--|

Statistical analysis description:

Primary efficacy analysis of overall survival between the three treatment arms carried out using Cox Proportional Hazards modelling

|   |  |
|---|--|
| Comparison groups                       | Gemcitabine and Capecitabine then Sequential GV1001 Therapy v Gemcitabine and Capecitabine Therapy |
| Number of subjects included in analysis | 708  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.05 <sup>[1]</sup>  |
| Method                                  | Regression, Cox  |
| Parameter estimate                      | Cox proportional hazard  |
| Point estimate                          | 1.19   |
| Confidence interval                     |  |
| level                                   | Other: 98.25 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.97   |
| upper limit                             | 1.48   |
| Variability estimate                    | Standard error of the mean   |

Notes:

[1] - Please note this is a family wise type I error for the full trial which includes multiple comparisons and formal interim analysis. The final P-value to determine significance of an experimental treatment over the control used a P-value of 0.02078.

| <b>Statistical analysis title</b> | Primary Efficacy Analysis Arm 1 Vs Arm 3 |
|-----------------------------------|--|
|-----------------------------------|--|

Statistical analysis description:

Primary efficacy analysis of overall survival between the three treatment arms carried out using Cox Proportional Hazards modelling

|   |  |
|---|--|
| Comparison groups                       | Gemcitabine and Capecitabine Therapy v Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
| Number of subjects included in analysis | 712  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.05 <sup>[2]</sup>  |
| Method                                  | Regression, Cox  |
| Parameter estimate                      | Cox proportional hazard  |
| Point estimate                          | 1.05   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | Other: 98.25 %             |
| sides                | 2-sided                    |
| lower limit          | 0.85                       |
| upper limit          | 1.29                       |
| Variability estimate | Standard error of the mean |

Notes:

[2] - Please note this is a family wise type I error for the full trial which includes multiple comparisons and formal interim analysis. The final P-value to determine significance of an experimental treatment over the control used a P-value of 0.02078.

## Secondary: Progression Free Survival

|   |                           |
|---|---------------------------|
| End point title   | Progression Free Survival |
| End point description:  |                           |
| End point type  | Secondary                 |
| End point timeframe:  |                           |
| Measured as the time from randomisation until progression or death by any cause |                           |

| End point values                 | Gemcitabine and Capecitabine Therapy | Gemcitabine and Capecitabine then Sequential GV1001 Therapy | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |  |
|----------------------------------|--------------------------------------|---|---|--|
| Subject group type               | Reporting group                      | Reporting group   | Reporting group   |  |
| Number of subjects analysed      | 358                                  | 350   | 354   |  |
| Units: Subjects                  |                                      |   |   |  |
| median (confidence interval 95%) | 6.35 (4.77 to 7.07)                  | 4.54 (4.34 to 4.61)   | 6.58 (5.03 to 7.27)                                     |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Progression Free Survival Arm 1 Vs Arm 2   |
| Comparison groups                       | Gemcitabine and Capecitabine Therapy v Gemcitabine and Capecitabine then Sequential GV1001 Therapy |
| Number of subjects included in analysis | 708  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.05   |
| Method                                  | Regression, Cox  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 1.5  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 1.26   |
| upper limit                             | 1.78   |

|   |  |
|---|--|
| Variability estimate                    | Standard error of the mean   |
|   |  |
| <b>Statistical analysis title</b>       | Progression Free Survival Arm 1 Vs Arm 3   |
| Comparison groups                       | Gemcitabine and Capecitabine Therapy v Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
| Number of subjects included in analysis | 712  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.05   |
| Method                                  | Regression, Cox  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 1  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.84   |
| upper limit                             | 1.19   |
| Variability estimate                    | Standard error of the mean   |

### Secondary: Best Overall Clinical Response

|  |                                |
|--|--------------------------------|
| End point title  | Best Overall Clinical Response |
| End point description:                                     |                                |
| End point type   | Secondary                      |
| End point timeframe:                                       |                                |
| From randomisation until death or competition of follow-up |                                |

| End point values            | Gemcitabine and Capecitabine Therapy | Gemcitabine and Capecitabine then Sequential GV1001 Therapy | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy | Full Analysis Set    |
|-----------------------------|--------------------------------------|---|---|----------------------|
| Subject group type          | Reporting group                      | Reporting group   | Reporting group   | Subject analysis set |
| Number of subjects analysed | 358                                  | 350   | 354   |                      |
| Units: Subjects             |                                      |   |   |                      |
| number (not applicable)     |                                      |   |   |                      |
| Missing                     | 28                                   | 19  | 26  | 73                   |
| Dead by 8 weeks             | 3                                    | 6   | 4   | 13                   |
| Dead other                  | 4                                    | 2   | 2   | 8                    |
| Progressive Disease         | 106                                  | 95  | 94  | 295                  |
| Stable Disease              | 154                                  | 197   | 173   | 524                  |
| Partial Response            | 60                                   | 30  | 52  | 142                  |
| Complete Response           | 3                                    | 1   | 3   | 7                    |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Best Overall Response Arm 1 Vs Arm 2   |
| Comparison groups                       | Gemcitabine and Capecitabine Therapy v Gemcitabine and Capecitabine then Sequential GV1001 Therapy |
| Number of subjects included in analysis | 708  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.01   |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Risk ratio (RR)  |
| Point estimate                          | 1.99   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 1.33   |
| upper limit                             | 2.98   |
| Variability estimate                    | Standard error of the mean   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Best Overall Response Arm 1 Vs Arm 3   |
| Comparison groups                       | Gemcitabine and Capecitabine Therapy v Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
| Number of subjects included in analysis | 712  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.46   |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Risk ratio (RR)  |
| Point estimate                          | 1.13   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.81   |
| upper limit                             | 1.58   |
| Variability estimate                    | Standard error of the mean   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs: Consent to last day of IMP administration/final study visit

SAEs (except deaths due to progressive disease): Consent until 28 days after last administration of trial treatment

After reporting period if AE/SAE possibly related to IMP

Adverse event reporting additional description:

ALL AEs recorded on CRF

ALL SAEs reported to ORION PVG via the documented reporting system

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

### Dictionary used

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

|                    |   |
|--------------------|---|
| Dictionary version | 3 |
|--------------------|---|

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Gemcitabine and Capecitabine Therapy |
|-----------------------|--------------------------------------|

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

|                       |   |
|-----------------------|---|
| Reporting group title | Gemcitabine and Capecitabine then Sequential GV1001 Therapy |
|-----------------------|---|

Reporting group description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

|                       |   |
|-----------------------|---|
| Reporting group title | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|-----------------------|---|

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

| Serious adverse events                            | Gemcitabine and Capecitabine Therapy | Gemcitabine and Capecitabine then Sequential GV1001 Therapy | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|---|--------------------------------------|---|---|
| Total subjects affected by serious adverse events |                                      |   |   |
| subjects affected / exposed                       | 134 / 358 (37.43%)                   | 147 / 350 (42.00%)  | 167 / 354 (47.18%)                                      |
| number of deaths (all causes)                     | 245                                  | 268   | 259   |
| number of deaths resulting from adverse events    | 10                                   | 13  | 10  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| Cancer pain   |                 |                 |                 |
| subjects affected / exposed   | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant ascites   |                 |                 |                 |
| subjects affected / exposed   | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all                     | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant ovarian cyst  |                 |                 |                 |
| subjects affected / exposed   | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to bone  |                 |                 |                 |
| subjects affected / exposed   | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to central nervous system                                |                 |                 |                 |
| subjects affected / exposed   | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Tumour invasion   |                 |                 |                 |
| subjects affected / exposed   | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Tumour pain   |                 |                 |                 |
| subjects affected / exposed   | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders  |                 |                 |                 |
| Circulatory collapse  |                 |                 |                 |



|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 2 / 4           |
| Deep vein thrombosis                            |                  |                 |                 |
| subjects affected / exposed                     | 11 / 358 (3.07%) | 8 / 350 (2.29%) | 7 / 354 (1.98%) |
| occurrences causally related to treatment / all | 10 / 22          | 14 / 20         | 14 / 36         |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Haemorrhage                                     |                  |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Hypertension                                    |                  |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Hypotension                                     |                  |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%) | 5 / 354 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 2 / 19          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                         |                  |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Phlebitis                                       |                  |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Thrombophlebitis                                |                  |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Thrombosis                                      |                  |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all      | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vena cava thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 4           |
| Surgical and medical procedures                      |                 |                 |                 |
| Pain management                                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Stent placement                                      |                 |                 |                 |
| subjects affected / exposed                          | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 2 / 358 (0.56%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 4           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest discomfort                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 4 / 358 (1.12%) | 1 / 350 (0.29%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all      | 1 / 8           | 0 / 4           | 1 / 16          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Chills   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 358 (0.28%) | 3 / 350 (0.86%) | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all      | 2 / 2           | 6 / 12          | 1 / 12          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Death   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 2 / 350 (0.57%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 6            | 0 / 0            |
| deaths causally related to treatment / all      | 2 / 2            | 0 / 6            | 0 / 0            |
| Device occlusion                                |                  |                  |                  |
| subjects affected / exposed                     | 9 / 358 (2.51%)  | 22 / 350 (6.29%) | 17 / 354 (4.80%) |
| occurrences causally related to treatment / all | 2 / 20           | 0 / 72           | 1 / 70           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Disease progression                             |                  |                  |                  |
| subjects affected / exposed                     | 25 / 358 (6.98%) | 31 / 350 (8.86%) | 22 / 354 (6.21%) |
| occurrences causally related to treatment / all | 2 / 51           | 1 / 112          | 0 / 86           |
| deaths causally related to treatment / all      | 0 / 24           | 0 / 52           | 0 / 32           |
| Fatigue   |                  |                  |                  |
| subjects affected / exposed                     | 3 / 358 (0.84%)  | 2 / 350 (0.57%)  | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 6 / 10           | 0 / 6            | 6 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| General physical health deterioration           |                  |                  |                  |
| subjects affected / exposed                     | 3 / 358 (0.84%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 4            | 0 / 0            |
| Influenza like illness                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mucosal inflammation                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 2            | 2 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oedema  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 2 / 350 (0.57%)  | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 6            | 2 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oedema peripheral                               |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 7 / 358 (1.96%)  | 2 / 350 (0.57%)  | 5 / 354 (1.41%)   |
| occurrences causally related to treatment / all | 2 / 14           | 2 / 4            | 3 / 24            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Pain  |                  |                  |                   |
| subjects affected / exposed                     | 4 / 358 (1.12%)  | 6 / 350 (1.71%)  | 4 / 354 (1.13%)   |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 22           | 0 / 16            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Pyrexia   |                  |                  |                   |
| subjects affected / exposed                     | 22 / 358 (6.15%) | 29 / 350 (8.29%) | 37 / 354 (10.45%) |
| occurrences causally related to treatment / all | 25 / 55          | 41 / 99          | 71 / 176          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Stent malfunction                               |                  |                  |                   |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Sudden death                                    |                  |                  |                   |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 2 / 354 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 8             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 8             |
| Immune system disorders                         |                  |                  |                   |
| Anaphylactic reaction                           |                  |                  |                   |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 4             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Hypersensitivity                                |                  |                  |                   |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 2 / 350 (0.57%)  | 3 / 354 (0.85%)   |
| occurrences causally related to treatment / all | 0 / 0            | 5 / 8            | 7 / 11            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Reproductive system and breast disorders        |                  |                  |                   |
| Scrotal oedema                                  |                  |                  |                   |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute pulmonary oedema                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute respiratory distress syndrome             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aspiration                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 9 / 358 (2.51%) | 5 / 350 (1.43%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all | 5 / 17          | 0 / 14          | 5 / 16          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 8           | 0 / 0           |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 4 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoptysis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hiccups   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Hydropneumothorax                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 0            |
| Hypoxia   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Interstitial lung disease                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pleural effusion                                |                  |                  |                  |
| subjects affected / exposed                     | 6 / 358 (1.68%)  | 3 / 350 (0.86%)  | 3 / 354 (0.85%)  |
| occurrences causally related to treatment / all | 2 / 14           | 0 / 16           | 0 / 12           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 2            | 2 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumothorax                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pulmonary embolism                              |                  |                  |                  |
| subjects affected / exposed                     | 19 / 358 (5.31%) | 26 / 350 (7.43%) | 16 / 354 (4.52%) |
| occurrences causally related to treatment / all | 11 / 40          | 19 / 82          | 14 / 64          |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 8            | 0 / 0            |
| Pulmonary oedema                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pulmonary thrombosis                            |                  |                  |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 3 / 350 (0.86%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all | 0 / 6           | 2 / 6           | 0 / 16          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mood altered                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Aspartate aminotransferase increased            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood albumin decreased                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood bilirubin increased                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 16          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood creatinine increased                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Blood glucose increased                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Body temperature increased                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoglobin decreased                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 2 / 12          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| International normalised ratio                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| International normalised ratio increased        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Liver function test abnormal                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urine output decreased                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| White blood cell count increased                |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Afferent loop syndrome                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 2 / 350 (0.57%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Laceration                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Narcotic intoxication                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Overdose  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural bile leak                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural haematoma                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pubis fracture                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Stent occlusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 2 / 350 (0.57%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transfusion reaction                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound complication                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 2 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| Arteriospasm coronary                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 358 (0.56%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 2 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 4           |
| Coronary artery occlusion                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Left ventricular failure                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 5 / 358 (1.40%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 5 / 10          | 1 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 2           | 1 / 4           |
| deaths causally related to treatment / all      | 2 / 2           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus bradycardia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Amnesia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ataxia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 1 / 350 (0.29%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           | 2 / 8           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 4           | 2 / 4           |
| Depressed level of consciousness                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 358 (0.28%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Epilepsy  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Facial palsy                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 2 / 350 (0.57%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 8           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Facial spasm                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lethargy  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Migraine  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parkinsonism                                    |                 |                 |                 |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peripheral motor neuropathy                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Presyncope                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Somnolence                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 2 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Syncope   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Transient ischaemic attack                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Unresponsive to stimuli                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 4 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood and lymphatic system disorders            |                  |                  |                  |
| Anaemia   |                  |                  |                  |
| subjects affected / exposed                     | 13 / 358 (3.63%) | 10 / 350 (2.86%) | 14 / 354 (3.95%) |
| occurrences causally related to treatment / all | 21 / 28          | 9 / 28           | 21 / 64          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Disseminated intravascular coagulation          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Febrile neutropenia                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 358 (0.56%)  | 3 / 350 (0.86%)  | 3 / 354 (0.85%)  |
| occurrences causally related to treatment / all | 4 / 4            | 6 / 6            | 6 / 12           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Leukopenia                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 2 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neutropenia                                     |                  |                  |                  |
| subjects affected / exposed                     | 4 / 358 (1.12%)  | 5 / 350 (1.43%)  | 8 / 354 (2.26%)  |
| occurrences causally related to treatment / all | 8 / 8            | 9 / 14           | 20 / 32          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thrombocytopenia                                |                  |                  |                  |
| subjects affected / exposed                     | 5 / 358 (1.40%)  | 2 / 350 (0.57%)  | 6 / 354 (1.69%)  |
| occurrences causally related to treatment / all | 11 / 12          | 4 / 4            | 13 / 24          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal disorders                      |                  |                  |                  |
| Abdominal distension                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal pain                                  |                  |                  |                  |
| subjects affected / exposed                     | 27 / 358 (7.54%) | 25 / 350 (7.14%) | 26 / 354 (7.34%) |
| occurrences causally related to treatment / all | 5 / 56           | 4 / 98           | 7 / 116          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal pain lower                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal pain upper                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 358 (1.40%)  | 1 / 350 (0.29%)  | 4 / 354 (1.13%)  |
| occurrences causally related to treatment / all | 2 / 10           | 0 / 4            | 1 / 12           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ascites   |                  |                  |                  |
| subjects affected / exposed                     | 20 / 358 (5.59%) | 20 / 350 (5.71%) | 17 / 354 (4.80%) |
| occurrences causally related to treatment / all | 0 / 43           | 2 / 88           | 0 / 92           |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 0            |
| Colitis   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 4 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colonic pseudo-obstruction                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Constipation                                    |                  |                  |                  |
| subjects affected / exposed                     | 13 / 358 (3.63%) | 10 / 350 (2.86%) | 12 / 354 (3.39%) |
| occurrences causally related to treatment / all | 8 / 30           | 6 / 28           | 2 / 52           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diarrhoea                                       |                  |                  |                  |
| subjects affected / exposed                     | 12 / 358 (3.35%) | 16 / 350 (4.57%) | 16 / 354 (4.52%) |
| occurrences causally related to treatment / all | 13 / 26          | 27 / 42          | 25 / 67          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal obstruction                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 4 / 350 (1.14%)  | 6 / 354 (1.69%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 14           | 0 / 24           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal stenosis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dyspepsia                                       |                  |                  |                  |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Enteritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 2 / 2           | 0 / 0           |
| Eruption  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis erosive                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal fistula                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 7 / 350 (2.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 6           | 1 / 20          | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal perforation                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 2 / 350 (0.57%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 8           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematemesis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| Impaired gastric emptying                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 1 / 350 (0.29%) | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           | 0 / 12          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| Large intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 2 / 350 (0.57%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 8           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mesenteric vein thrombosis                      |                 |                 |                 |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Nausea  |                 |                  |                  |
| subjects affected / exposed                     | 8 / 358 (2.23%) | 18 / 350 (5.14%) | 17 / 354 (4.80%) |
| occurrences causally related to treatment / all | 11 / 16         | 29 / 61          | 22 / 71          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Obstruction gastric                             |                 |                  |                  |
| subjects affected / exposed                     | 5 / 358 (1.40%) | 10 / 350 (2.86%) | 5 / 354 (1.41%)  |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 40           | 0 / 20           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 8            | 0 / 0            |
| Oesophageal varices haemorrhage                 |                 |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Pancreatitis                                    |                 |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 2 / 350 (0.57%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4            | 0 / 0            |
| Peptic ulcer perforation                        |                 |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4            | 0 / 0            |
| Peritoneal perforation                          |                 |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0            | 0 / 0            |
| Rectal haemorrhage                              |                 |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 3 / 350 (0.86%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 10           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Small intestinal haemorrhage                    |                 |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small intestinal obstruction                    |                  |                  |                  |
| subjects affected / exposed                     | 4 / 358 (1.12%)  | 1 / 350 (0.29%)  | 4 / 354 (1.13%)  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 4            | 0 / 16           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stomatitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 3 / 358 (0.84%)  | 1 / 350 (0.29%)  | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 6 / 6            | 2 / 4            | 2 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Upper gastrointestinal haemorrhage              |                  |                  |                  |
| subjects affected / exposed                     | 3 / 358 (0.84%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 0            |
| Vomiting  |                  |                  |                  |
| subjects affected / exposed                     | 28 / 358 (7.82%) | 25 / 350 (7.14%) | 33 / 354 (9.32%) |
| occurrences causally related to treatment / all | 26 / 59          | 27 / 95          | 43 / 144         |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatobiliary disorders                         |                  |                  |                  |
| Bile duct obstruction                           |                  |                  |                  |
| subjects affected / exposed                     | 8 / 358 (2.23%)  | 7 / 350 (2.00%)  | 7 / 354 (1.98%)  |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 30           | 0 / 32           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bile duct stenosis                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 4 / 350 (1.14%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 14           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Biliary dilatation                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 4 / 354 (1.13%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 16           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholangitis                                     |                  |                  |                  |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 12 / 358 (3.35%) | 9 / 350 (2.57%) | 11 / 354 (3.11%) |
| occurrences causally related to treatment / all | 8 / 26           | 0 / 38          | 0 / 50           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Cholecystitis                                   |                  |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 3 / 350 (0.86%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 8           | 2 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Cholelithiasis                                  |                  |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Gallbladder obstruction                         |                  |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 8           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 4           | 0 / 0            |
| Hepatic failure                                 |                  |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0           | 0 / 0            |
| Hepatic function abnormal                       |                  |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 1 / 350 (0.29%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Hepatic pain                                    |                  |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Hyperbilirubinaemia                             |                  |                 |                  |
| subjects affected / exposed                     | 6 / 358 (1.68%)  | 4 / 350 (1.14%) | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 14          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Jaundice  |                  |                 |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 358 (0.84%) | 0 / 350 (0.00%) | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           | 1 / 12          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Jaundice cholestatic                            |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 6 / 350 (1.71%) | 8 / 354 (2.26%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 20          | 0 / 36          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4           | 0 / 0           |
| Liver disorder                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Perforation bile duct                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Portal vein thrombosis                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 2 / 350 (0.57%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 2 / 4           | 2 / 10          | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Blister   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 3 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palmar-plantar erythrodysaesthesia syndrome     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Panniculitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Plantar erythema                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rash  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 3 / 350 (0.86%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 2 / 2           | 5 / 8           | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rash generalised                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rash pruritic                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 2 / 350 (0.57%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 4           | 3 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Swelling face                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 4 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Dysuria   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 0 / 350 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           | 1 / 8           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 4           |
| Renal failure acute                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 2 / 350 (0.57%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 358 (0.56%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract obstruction                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 2 / 350 (0.57%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 6           | 0 / 16          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bone pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal pain                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal sepsis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4           | 0 / 0           |
| Anal abscess                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Bacteraemia                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bacterial infection                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Biliary sepsis                                  |                  |                  |                  |
| subjects affected / exposed                     | 16 / 358 (4.47%) | 16 / 350 (4.57%) | 16 / 354 (4.52%) |
| occurrences causally related to treatment / all | 2 / 40           | 12 / 72          | 4 / 98           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 4            | 0 / 4            |
| Biliary tract infection                         |                  |                  |                  |
| subjects affected / exposed                     | 3 / 358 (0.84%)  | 1 / 350 (0.29%)  | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 4 / 6            | 0 / 2            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchopneumonia                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 2 / 2            | 0 / 0            |
| Cellulitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 12 / 358 (3.35%) | 4 / 350 (1.14%)  | 6 / 354 (1.69%)  |
| occurrences causally related to treatment / all | 5 / 26           | 6 / 10           | 5 / 23           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholangitis suppurative                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 0            |
| Clostridial infection                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%)  | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Device related infection                        |                  |                  |                  |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 2 / 350 (0.57%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 8           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Diverticulitis                                  |                  |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Escherichia sepsis                              |                  |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 3 / 350 (0.86%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 12          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Gallbladder abscess                             |                  |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 0 / 350 (0.00%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Gastroenteritis                                 |                  |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%)  | 1 / 350 (0.29%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Infection                                       |                  |                 |                  |
| subjects affected / exposed                     | 16 / 358 (4.47%) | 4 / 350 (1.14%) | 12 / 354 (3.39%) |
| occurrences causally related to treatment / all | 20 / 36          | 1 / 18          | 9 / 56           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Infectious peritonitis                          |                  |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Klebsiella infection                            |                  |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%)  | 0 / 350 (0.00%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Klebsiella sepsis                               |                  |                 |                  |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 4            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Liver abscess                                   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 2 / 350 (0.57%)  | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 8            | 0 / 12          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 4           |
| Lower respiratory tract infection               |                 |                  |                 |
| subjects affected / exposed                     | 6 / 358 (1.68%) | 11 / 350 (3.14%) | 9 / 354 (2.54%) |
| occurrences causally related to treatment / all | 10 / 12         | 8 / 34           | 10 / 44         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4            | 0 / 0           |
| Mastoiditis                                     |                 |                  |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%)  | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Neutropenic infection                           |                 |                  |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%)  | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Neutropenic sepsis                              |                 |                  |                 |
| subjects affected / exposed                     | 8 / 358 (2.23%) | 3 / 350 (0.86%)  | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 16 / 16         | 6 / 8            | 4 / 8           |
| deaths causally related to treatment / all      | 2 / 2           | 0 / 0            | 0 / 0           |
| Opportunistic infection                         |                 |                  |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 4            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4            | 0 / 0           |
| Oral candidiasis                                |                 |                  |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Paronychia                                      |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis bacterial                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pharyngitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 5 / 350 (1.43%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all | 2 / 6           | 3 / 16          | 4 / 20          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 6           | 0 / 0           |
| Pneumonia klebsiella                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural infection                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pseudomonas infection                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                 |                 |                 |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 2 / 354 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Sepsis  |                 |                 |                  |
| subjects affected / exposed                     | 6 / 358 (1.68%) | 8 / 350 (2.29%) | 13 / 354 (3.67%) |
| occurrences causally related to treatment / all | 0 / 12          | 10 / 20         | 9 / 56           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 8            |
| Septic shock                                    |                 |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4            |
| Skin infection                                  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Staphylococcal sepsis                           |                 |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Stent related infection                         |                 |                 |                  |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 4 / 350 (1.14%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 10          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4            |
| Streptococcal sepsis                            |                 |                 |                  |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Tonsillitis                                     |                 |                 |                  |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Upper respiratory tract infection               |                 |                 |                  |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%)  | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0            | 4 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Urinary tract infection                         |                 |                  |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 3 / 350 (0.86%)  | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 3 / 6           | 2 / 10           | 0 / 12          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Viral infection                                 |                 |                  |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%)  | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Wound abscess                                   |                 |                  |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Wound infection                                 |                 |                  |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%)  | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 4            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                  |                 |
| Anorexia  |                 |                  |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%)  | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 4 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Decreased appetite                              |                 |                  |                 |
| subjects affected / exposed                     | 4 / 358 (1.12%) | 3 / 350 (0.86%)  | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 4 / 8           | 0 / 10           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Dehydration                                     |                 |                  |                 |
| subjects affected / exposed                     | 5 / 358 (1.40%) | 10 / 350 (2.86%) | 4 / 354 (1.13%) |
| occurrences causally related to treatment / all | 4 / 10          | 6 / 32           | 0 / 16          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Diabetes mellitus                               |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 358 (0.00%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 1 / 350 (0.29%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| Gout  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypercalcaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 358 (0.84%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 4           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 358 (0.28%) | 7 / 350 (2.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 4 / 20          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 3 / 350 (0.86%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 10          | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypokalaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 358 (0.56%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemic syndrome                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 358 (0.28%) | 0 / 350 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oral intake reduced                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 358 (0.00%) | 0 / 350 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Gemcitabine and Capecitabine Therapy | Gemcitabine and Capecitabine then Sequential GV1001 Therapy | Concurrent Gemcitabine, Capecitabine and GV1001 Therapy |
|---|--------------------------------------|---|---|
| Total subjects affected by non-serious adverse events |                                      |   |   |
| subjects affected / exposed                           | 320 / 358 (89.39%)                   | 306 / 350 (87.43%)  | 325 / 354 (91.81%)                                      |
| General disorders and administration site conditions  |                                      |   |   |
| Fatigue   |                                      |   |   |
| subjects affected / exposed                           | 69 / 358 (19.27%)                    | 63 / 350 (18.00%)   | 61 / 354 (17.23%)                                       |
| occurrences (all)                                     | 105                                  | 103   | 105   |
| Gastrointestinal disorders                            |                                      |   |   |
| Nausea  |                                      |   |   |
| subjects affected / exposed                           | 60 / 358 (16.76%)                    | 52 / 350 (14.86%)   | 57 / 354 (16.10%)                                       |
| occurrences (all)                                     | 101                                  | 87  | 99  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 08 January 2007  | SUBSTANTIAL AMENDMENT (MREC 01)<br>- Change in the content of clinical Kit 1 (include one more vial of Leukine (GM-CSF) and one less vial of Bacteriostatic Water)<br>- Change in label text to clarify the storage conditions and in-use shelf-life for GV1001 and Leukine after reconstitution<br>Both reflected in minor changes in the protocol  |
| 05 March 2007    | SUBSTANTIAL AMENDMENT (MREC 02)<br>- Changes to the protocol<br>- Submission of Investigators Brochure (IB) to replace SmPC  |
| 05 March 2007    | SUBSTANTIAL AMENDMENT (MREC 03)<br>- Changes to Protocol (Submitted to both MHRA and MREC in order to seek approval of amendment 2 to Protocol version 5)<br>- Change in Clinical Trial Agreement (Chief Investigator changed from Professor J Neoptolemos to Dr G Middleton, Principal Investigator has changed from Dr G Middleton to Professor J Neoptolemos)   |
| 08 March 2007    | SUBSTANTIAL AMENDMENT (MREC 04)<br>Protocol Changes<br>- Deletion of University as a co-sponsor<br>- Deletion of University as a co-sponsor on Patient Information Sheet<br>Clinical Trial Agreement Changes<br>- Deletion of University as a co-sponsor   |
| 06 July 2007     | SUBSTANTIAL AMENDMENT (MREC 06)<br>- Changes to the Protocol<br>- Change in the Clinical Trial Application<br>- Change in the MREC Parts A&B<br>- Change of Investigators<br>- Addition of new sites<br>- Update of IMPD of GV1001 to extend the shelf-life and change of the specifications   |
| 20 December 2007 | SUBSTANTIAL AMENDMENT (MREC 07)<br>- Changes to the Protocol:<br>Change in GV1001 Kit 1 design<br>Change of sample schedule for immunomonitoring<br>Change of type of documents to be reviewed by LCTU before randomisation of a patient<br>- Change in the Clinical Trial Application – Addition of new sites<br>- Change in the MREC Parts A&B – Addition of new sites                                     |
| 01 May 2008      | SUBSTANTIAL AMENDMENT (MREC 08)<br>- Change of PI due to maternity leave – Dr Pippa Corrie from Addenbrooke's hospital will be on maternity leave from the 06/05/2008 to the 04/01/2008. The new PI for the site will be Dr Hugo Ford.<br>- Addition of new site – Weston General Hospital in Weston-Super-Mare has joined the list of sites on the TeloVac trial. The PI for this site is Dr Serena Hilman. |
| 20 May 2008      | SUBSTANTIAL AMENDMENT (MREC 09)<br>- Change of PI due to maternity leave - Dr Archer from Portsmouth Hospital will be on maternity leave until October. The new PI will be Ann O'Callaghan<br>- Change of PI due to Dr Ostrowski retiring 0 Dr Ostrowski will be replaced by Dr Stubbings at Norfolk and Norwich   |

|                  |   |
|------------------|---|
| 10 July 2008     | SUBSTANTIAL AMENDMENT (MREC 10)<br>- Change of PI at James Paget Hospital<br>- Addition of site namely Alexandra Hospital<br>- Notification of update to the GV1001 IB (for information only)   |
| 17 November 2008 | SUBSTANTIAL AMENDMENT (MREC 11)<br>- Notification of update to the Xeloda (capecitabine) IB<br>- Notification of change of Principal Investigator   |
| 27 February 2009 | MINOR AMENDMENT (MREC) 12 - Information only<br>- Submission of additional label text provided for capecitabine by Roche  |
| 05 August 2009   | SUBSTANTIAL AMENDMENT (MREC 13)<br>- Change in PI at 3 sites: Norfolk and Norwich, Churchill and Yeovil District Hospital   |
| 18 January 2010  | MINOR AMENDMENT (MREC 14)<br>- Updated IBs (information only): Xeloda v10 and v11   |
| 02 February 2010 | SUBSTANTIAL AMENDMENT (MREC 15&16)<br>- Change to Patient Diary and Skin Test Ruler<br>- Change in PI at Torbay Hospital  |
| 24 June 2010     | MINOR AMENDMENT (MREC 17) - Information Only<br>- Capecitabine diary footer altered to state version 3<br>- GV1001 IB v6 submitted for information  |
| 04 August 2010   | SUBSTANTIAL AMENDMENT (MREC 18)<br>- Protocol amended to allow for treatment breaks for patients<br>- Administrative changes for protocol (re-ordering sections).<br>- Notification of change of name from Cookridge Hospital to St James (named as Cookridge on original CTA).<br>- Information sheet and informed consent form re-numbered as version 8 to avoid confusion. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption   | Restart date |
|-------------|--|--------------|
| 26 May 2011 | There was evidence that patients receiving vaccine treatment alone (Arm 2) had a poorer outcome than patients receiving standard chemotherapy treatment and there was no evidence of a survival benefit from the addition of vaccine to chemotherapy compared to chemotherapy alone. The MHRA and Ethics were first informed of Urgent Safety Measures taken on 24/05/2011 that resulted in suspension of recruitment to Arm 2 of the trial. Given the advanced stage of the trial and the relatively small number of patients needed to completed target recruitment, the recommendation of the DMC and TSC (26/05/2011) was to close the TeloVac trial to further recruitment on 27/05/2011. | -            |

Notes:

## Limitations and caveats

None reported

