



## Clinical trial results:

### RAMSES / FLOT7

## Perioperative RAMucirumab in combination with FLOT versus FLOT alone for reSEctable eSophagogastric adenocarcinoma RAMSES - a phase II/III trial of the AIO

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-003118-26 |
| Trial protocol           | DE IT          |
| Global end of trial date | 20 June 2022   |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 23 September 2023 |
| First version publication date | 23 September 2023 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | RAMSES/FLOT7 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02661971 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest  |
| Sponsor organisation address | Steinbacher Hohl 2-26, Frankfurt am Main Mitte-West, Frankfurt am Main, Germany, 60488                        |
| Public contact               | Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest, info@ikf-khnw.de |
| Scientific contact           | Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest, info@ikf-khnw.de |

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                       | 22 July 2022 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 20 June 2022 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The aim of this trial was to evaluate the efficacy and safety of the combination of perioperative FLOT with the anti-VEGFR antibody ramucirumab in patients with resectable esophagogastric adenocarcinoma.

Protection of trial subjects:

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the AMG (Arzneimittelgesetz), the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The trial was authorized/approved by the competent authority (Paul-Ehrlich-Institut, PEI) and the competent ethics committee responsible for the trial ("federführende Ethikkommission"). Before recruitment into the clinical trial, each patient was informed that participation in the study is completely voluntary, and that he or she may withdraw his or her participation in the trial at any time without any declaration of reasons, which will not lead to any disadvantage for the respective patient. The eligibility of a new patient was determined by the local investigator during regular clinical visits. The examinations for the study and the inclusion of the patient were done after detailed written and oral education about aims, methods, anticipated benefits and potential hazards of the study by use of the informed consent forms and after given written consent of the patient. Safety of FLOT/Ramucirumab was monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported. An independent data safety and monitoring board (DSMB) was responsible for assessment of reports summarizing safety data or study results and gave recommendations for planned protocol amendments.

Background therapy: -

Evidence for comparator:

FLOT, a docetaxel-based triple combination consisting of 5-FU, leucovorin, oxaliplatin and docetaxel, is one of the most intensively evaluated regimen for gastric and GEJ cancer. It has been evaluated in the perioperative setting, the metastatic and limited metastatic settings, in elderly and in operable patients. FLOT is regarded as a standard chemotherapy regimen for gastric cancer in Germany.

Ramucirumab is a human monoclonal antibody that specifically binds VEGF-R2. The binding of ramucirumab to VEGF-R2 prevents its interaction with the activating ligands VEGF-A, VEGF-C, and VEGF-D. Ramucirumab was approved for advanced or metastatic esophagogastric adenocarcinoma after previous chemotherapy.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 12 July 2016 |
| 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 | Germany: 170 |
| Country: Number of subjects enrolled | Italy: 10    |
| Worldwide total number of subjects   | 180          |
| EEA total number of subjects         | 180          |

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)                      | 130 |
| From 65 to 84 years                       | 50  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 180 patients for enrolled the phase II part between JULY 2016 and NOV 2019 in 50 centres in Germany and 10 centres in Italy. Approx. 758 additional patients were planned for phase III. However, the trial was terminated after phase II part and not transitioned into phase III.

### Pre-assignment

Screening details:

Patients with locally advanced adenocarcinoma of the stomach and gastroesophageal junction type I-III (i.e. cT2 any N or any T N-positive) with exclusion of distant metastases were included in this trial. Due to safety concerns, patients with GEJ type I as well as with planned transthoracic esophagectomy at study entry were excluded after NOV2017

### Period 1

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

### Arms

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

Arm description:

4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43, plus additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase

|  |   |
|--|---|
| Arm type                               | Active comparator   |
| Investigational medicinal product name | Docetaxel   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection/infusion |
| Routes of administration               | Infusion  |

Dosage and administration details:

Administration 50 mg/m<sup>2</sup>, iv over 1 h d1, d15, d29, d43 pre- and post-operative

|  |   |
|--|---|
| Investigational medicinal product name | Oxaliplatin   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection/infusion |
| Routes of administration               | Infusion , Injection  |

Dosage and administration details:

85 mg/m<sup>2</sup> in 500 ml 5% Glucose, iv over 2h

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Leucovorin                      |
| Investigational medicinal product code |                                 |
| Other name                             | folinic acid                    |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Infusion , Injection            |

Dosage and administration details:

200 mg/m<sup>2</sup> in 250 ml NaCl 0.9%, iv over 30 min

|   |                                 |
|---|---------------------------------|
| Investigational medicinal product name                                      | 5-Fluorouracil                  |
| Investigational medicinal product code                                      |                                 |
| Other name  | 5-FU                            |
| Pharmaceutical forms  | Solution for injection/infusion |
| Routes of administration  | Injection , Infusion            |
| Dosage and administration details:<br>2600 mg/m <sup>2</sup> , iv over 24 h |                                 |

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Arm B - FLOT/Ramucirumab |
|------------------|--------------------------|

Arm description:

Patients received Ramucirumab at indicated days as well as the FLOT regimen, which was administered identical to Arm A as described above. Surgery in Arm B was planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients received FLOT + Ramucirumab for 8 weeks in the post-operative treatment phase followed by 16 additional doses of Ramucirumab as a monotherapy every 2 weeks.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Docetaxel   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection/infusion |
| Routes of administration               | Infusion  |

Dosage and administration details:

Administration 50 mg/m<sup>2</sup>, iv over 1 h d1, d15, d29, d43 pre- and post-operative

|  |   |
|--|---|
| Investigational medicinal product name | Oxaliplatin   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection/infusion |
| Routes of administration               | Infusion , Injection  |

Dosage and administration details:

85 mg/m<sup>2</sup> in 500 ml 5% Glucose, iv over 2h

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Leucovorin                      |
| Investigational medicinal product code |                                 |
| Other name                             | folinic acid                    |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Infusion , Injection            |

Dosage and administration details:

200 mg/m<sup>2</sup> in 250 ml NaCl 0.9%, iv over 30 min

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | 5-Fluorouracil                  |
| Investigational medicinal product code |                                 |
| Other name                             | 5-FU                            |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Infusion , Injection            |

Dosage and administration details:

2600 mg/m<sup>2</sup>, iv over 24 h

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Ramucirumab                           |
| Investigational medicinal product code | SUB32795                              |
| Other name                             | Cyramza                               |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Infusion                              |

| <b>Number of subjects in period 1</b>              | Arm A - FLOT     | Arm B - FLOT/Ramucirumab |
|--|------------------|--------------------------|
| Started  | 91               | 89                       |
| started pre-OP treatment                           | 90               | 88                       |
| underwent surgery                                  | 85               | 87                       |
| started post-OP treatment                          | 57               | 64                       |
| started maintenance                                | 0 <sup>[1]</sup> | 43                       |
| Completed  | 46               | 24                       |
| Not completed                                      | 45               | 65                       |
| Consent withdrawn by subject                       | 13               | 18                       |
| Physician decision                                 | 1                | 3                        |
| death  | 3                | 9                        |
| Adverse event, non-fatal                           | 14               | 19                       |
| unplanned hospitalization                          | -                | 1                        |
| histological report from 26.09.2017 declared no ca | 1                | -                        |
| Lost to follow-up                                  | 1                | -                        |
| Sponsor decision                                   | -                | 4                        |
| Lack of efficacy                                   | 12               | 11                       |

Notes:

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

Justification: No maintenance phase was planned in Arm A

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Arm A - FLOT |
|-----------------------|--------------|

Reporting group description:

4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43, plus additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Arm B - FLOT/Ramucirumab |
|-----------------------|--------------------------|

Reporting group description:

Patients received Ramucirumab at indicated days as well as the FLOT regimen, which was administered identical to Arm A as described above. Surgery in Arm B was planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients received FLOT + Ramucirumab for 8 weeks in the post-operative treatment phase followed by 16 additional doses of Ramucirumab as a monotherapy every 2 weeks.

| Reporting group values   | Arm A - FLOT | Arm B - FLOT/Ramucirumab | Total |
|--|--------------|--------------------------|-------|
| Number of subjects   | 91           | 89                       | 180   |
| Age categorical  |              |                          |       |
| Units: Subjects  |              |                          |       |
| In utero   |              |                          | 0     |
| Preterm newborn infants (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   |              |                          |       |
| Units: years   |              |                          |       |
| median   | 51           | 60                       |       |
| full range (min-max)   | 35 to 70     | 36 to 70                 | -     |
| Gender categorical   |              |                          |       |
| Units: Subjects  |              |                          |       |
| Female   | 24           | 24                       | 48    |
| Male   | 67           | 65                       | 132   |
| ECOG   |              |                          |       |
| Units: Subjects  |              |                          |       |
| ECOG 0   | 73           | 59                       | 132   |
| ECOG 1   | 18           | 30                       | 48    |
| Primary localisation   |              |                          |       |
| Adenocarcinomas of the gastro-esophageal junction were classified according to the Siewert classification as tumors having their center 5 cm proximal or distal of the anatomical cardia |              |                          |       |
| Units: Subjects  |              |                          |       |
| GEJ type I   | 12           | 16                       | 28    |
| GEJ type II  | 29           | 24                       | 53    |
| GEJ type III   | 7            | 8                        | 15    |

|  |    |    |     |
|--|----|----|-----|
| Stomach, corpus or antrum  | 43 | 41 | 84  |
| cT stage   |    |    |     |
| Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor-node-metastasis classification  |    |    |     |
| Units: Subjects  |    |    |     |
| T1   | 0  | 1  | 1   |
| T2   | 17 | 13 | 30  |
| T3   | 70 | 67 | 137 |
| T4   | 2  | 2  | 4   |
| T4a  | 2  | 6  | 8   |
| cN stage   |    |    |     |
| Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor-node-metastasis classification. |    |    |     |
| Units: Subjects  |    |    |     |
| N-   | 23 | 17 | 40  |
| N+   | 68 | 72 | 140 |
| Barrett's carcinoma  |    |    |     |
| Barrett's carcinoma was defined as the presence of Barrett's mucosa in tumors of the gastro-esophageal junction as assessed by either baseline endoscopy or pathological examination. Stomach tumors were automatically regarded non-Barrett |    |    |     |
| Units: Subjects  |    |    |     |
| Yes  | 10 | 8  | 18  |
| No   | 72 | 77 | 149 |
| Unclear  | 6  | 4  | 10  |
| Missing  | 3  | 0  | 3   |
| Lauren's type  |    |    |     |
| Units: Subjects  |    |    |     |
| Diffuse  | 36 | 30 | 66  |
| Intestinal   | 31 | 33 | 64  |
| Mixed  | 11 | 9  | 20  |
| Not evaluable acc. to Lauren   | 8  | 14 | 22  |
| Missing  | 5  | 3  | 8   |
| Signet-ring cells  |    |    |     |
| Defined as the presence of any signet-ring cells.  |    |    |     |
| Units: Subjects  |    |    |     |
| Yes  | 39 | 33 | 72  |
| No   | 50 | 54 | 104 |
| Missing  | 2  | 2  | 4   |
| Grading according to WHO   |    |    |     |
| WHO grading increases with the lack of cellular differentiation, reflecting how much the tumor cells differ from the cells of the normal tissue they have originated from  |    |    |     |
| Units: Subjects  |    |    |     |
| G1   | 4  | 3  | 7   |
| G2   | 22 | 27 | 49  |
| G3   | 58 | 54 | 112 |
| Missing  | 7  | 5  | 12  |
| HER2 status  |    |    |     |
| Units: Subjects  |    |    |     |
| HER2 positive  | 2  | 0  | 2   |
| HER2 negative  | 87 | 85 | 172 |

|         |   |   |   |
|---------|---|---|---|
| Missing | 2 | 4 | 6 |
|---------|---|---|---|

## Subject analysis sets

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | mITT Arm A                  |
| Subject analysis set type  | Modified intention-to-treat |

Subject analysis set description:

includes all patients in Arm A who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | mITT Arm B                  |
| Subject analysis set type  | Modified intention-to-treat |

Subject analysis set description:

includes all patients in Arm B who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

| Reporting group values  | mITT Arm A | mITT Arm B |  |
|---|------------|------------|--|
| Number of subjects  | 79         | 73         |  |
| 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  |            |            |  |
| median  | 59         | 61         |  |
| full range (min-max)  | 35 to 70   | 36 to 70   |  |
| Gender categorical<br>Units: Subjects   |            |            |  |
| Female  | 23         | 23         |  |
| Male  | 56         | 50         |  |
| ECOG<br>Units: Subjects   |            |            |  |
| ECOG 0  | 63         | 50         |  |
| ECOG 1  | 16         | 23         |  |
| Primary localisation  |            |            |  |
| Adenocarcinomas of the gastro-esophageal junction were classified according to the Siewert classification as tumors having their center 5 cm proximal or distal of the anatomical cardia  |            |            |  |
| Units: Subjects   |            |            |  |
| GEJ type I  | 0          | 0          |  |
| GEJ type II   | 29         | 24         |  |
| GEJ type III  | 7          | 8          |  |
| Stomach, corpus or antrum   | 43         | 41         |  |

|  |    |    |  |
|--|----|----|--|
| cT stage   |    |    |  |
| Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor-node-metastasis classification  |    |    |  |
| Units: Subjects  |    |    |  |
| T1   | 0  | 1  |  |
| T2   | 15 | 12 |  |
| T3   | 60 | 54 |  |
| T4   | 2  | 1  |  |
| T4a  | 2  | 5  |  |
| cN stage   |    |    |  |
| Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor-node-metastasis classification. |    |    |  |
| Units: Subjects  |    |    |  |
| N-   | 20 | 15 |  |
| N+   | 59 | 58 |  |
| Barrett's carcinoma  |    |    |  |
| Barrett's carcinoma was defined as the presence of Barrett's mucosa in tumors of the gastro-esophageal junction as assessed by either baseline endoscopy or pathological examination. Stomach tumors were automatically regarded non-Barrett |    |    |  |
| Units: Subjects  |    |    |  |
| Yes  | 2  | 4  |  |
| No   | 68 | 67 |  |
| Unclear  | 6  | 2  |  |
| Missing  | 3  | 0  |  |
| Lauren's type  |    |    |  |
| Units: Subjects  |    |    |  |
| Diffuse  | 36 | 28 |  |
| Intestinal   | 24 | 24 |  |
| Mixed  | 9  | 8  |  |
| Not evaluable acc. to Lauren   | 7  | 11 |  |
| Missing  | 3  | 2  |  |
| Signet-ring cells  |    |    |  |
| Defined as the presence of any signet-ring cells.  |    |    |  |
| Units: Subjects  |    |    |  |
| Yes  | 37 | 31 |  |
| No   | 40 | 41 |  |
| Missing  | 2  | 1  |  |
| Grading according to WHO   |    |    |  |
| WHO grading increases with the lack of cellular differentiation, reflecting how much the tumor cells differ from the cells of the normal tissue they have originated from  |    |    |  |
| Units: Subjects  |    |    |  |
| G1   | 2  | 3  |  |
| G2   | 17 | 17 |  |
| G3   | 53 | 49 |  |
| Missing  | 7  | 4  |  |
| HER2 status  |    |    |  |
| Units: Subjects  |    |    |  |
| HER2 positive  | 0  | 0  |  |
| HER2 negative  | 77 | 69 |  |
| Missing  | 2  | 4  |  |



## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Arm A - FLOT |
|-----------------------|--------------|

Reporting group description:

4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43, plus additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Arm B - FLOT/Ramucirumab |
|-----------------------|--------------------------|

Reporting group description:

Patients received Ramucirumab at indicated days as well as the FLOT regimen, which was administered identical to Arm A as described above. Surgery in Arm B was planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients received FLOT + Ramucirumab for 8 weeks in the post-operative treatment phase followed by 16 additional doses of Ramucirumab as a monotherapy every 2 weeks.

|                            |            |
|----------------------------|------------|
| Subject analysis set title | mITT Arm A |
|----------------------------|------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

includes all patients in Arm A who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

|                            |            |
|----------------------------|------------|
| Subject analysis set title | mITT Arm B |
|----------------------------|------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

includes all patients in Arm B who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

### Primary: Pathological complete and subtotal response

|                 |   |
|-----------------|---|
| End point title | Pathological complete and subtotal response |
|-----------------|---|

End point description:

The pathological complete response (pCR) and subtotal response (pSR) rate was chosen as primary endpoint for the phase II part of the trial and was defined as the proportion of patients with pCR as evaluated blinded by central pathologist referring to the total number of patients of the

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

End point timeframe:

The relevant time point for the primary study endpoint was reached upon completion of surgery. Patients with a pCR or pSR at this timepoint added to the rate of the primary endpoint.

| End point values            | Arm A - FLOT    | Arm B - FLOT/Ramucirumab | mITT Arm A           | mITT Arm B           |
|-----------------------------|-----------------|--------------------------|----------------------|----------------------|
| Subject group type          | Reporting group | Reporting group          | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 91              | 89                       | 79                   | 73                   |
| Units: Subjects             |                 |                          |                      |                      |
| Yes                         | 28              | 24                       | 23                   | 19                   |
| No                          | 63              | 65                       | 56                   | 54                   |

## Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Fisher Exact Test       |
| Comparison groups                       | mITT Arm A v mITT Arm B |
| Number of subjects included in analysis | 152                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.719                 |
| Method                                  | Fisher exact            |

## Secondary: Margin-free (R0) resection

|   |                            |
|---|----------------------------|
| End point title   | Margin-free (R0) resection |
| End point description:<br>R0 resection rate was defined as the percentage of patients achieving a R0 (margin-free) resection referring to the total number of patients randomized into the respective treatment arm |                            |
| End point type  | Secondary                  |
| End point timeframe:<br>The relevant time point was reached upon completion of surgery  |                            |

| End point values            | Arm A - FLOT    | Arm B - FLOT/Ramucirumab | mITT Arm A           | mITT Arm B           |
|-----------------------------|-----------------|--------------------------|----------------------|----------------------|
| Subject group type          | Reporting group | Reporting group          | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 91              | 89                       | 79                   | 73                   |
| Units: Subjects             |                 |                          |                      |                      |
| Yes                         | 75              | 86                       | 65                   | 70                   |
| No                          | 16              | 3                        | 14                   | 3                    |

## Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Fisher Exact Test       |
| Comparison groups                       | mITT Arm A v mITT Arm B |
| Number of subjects included in analysis | 152                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.009                 |
| Method                                  | Fisher exact            |

## Secondary: Disease-free survival

|                        |                       |
|------------------------|-----------------------|
| End point title        | Disease-free survival |
| End point description: |                       |

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:<br>defined as time from randomization to disease progression, relapse or death |           |

| End point values                 | Arm A - FLOT        | Arm B - FLOT/Ramucirumab | mITT Arm A           | mITT Arm B               |
|----------------------------------|---------------------|--------------------------|----------------------|--------------------------|
| Subject group type               | Reporting group     | Reporting group          | Subject analysis set | Subject analysis set     |
| Number of subjects analysed      | 91                  | 89                       | 79                   | 73                       |
| Units: month                     |                     |                          |                      |                          |
| median (confidence interval 95%) | 20.5 (15.0 to 38.7) | 31.3 (22.4 to 46)        | 20.5 (12.7 to 42.7)  | 31.9 (23.9 to 999999999) |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | DFS mITT/RAMSES Final analysis_ITT_22.07.2022_DFS.bmp |
|-----------------------------------|---|

### Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Log Rank Test           |
| Comparison groups                       | mITT Arm B v mITT Arm A |
| Number of subjects included in analysis | 152                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.248                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.765                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.48                    |
| upper limit                             | 1.21                    |

### Secondary: Overall survival

|   |                  |
|---|------------------|
| End point title   | Overall survival |
| End point description:  |                  |
| End point type  | Secondary        |
| End point timeframe:<br>OS defined as time from randomization to death; |                  |

| End point values                 | Arm A - FLOT           | Arm B - FLOT/Ramucirumab | mITT Arm A             | mITT Arm B               |
|----------------------------------|------------------------|--------------------------|------------------------|--------------------------|
| Subject group type               | Reporting group        | Reporting group          | Subject analysis set   | Subject analysis set     |
| Number of subjects analysed      | 91                     | 89                       | 79                     | 73                       |
| Units: month                     |                        |                          |                        |                          |
| median (confidence interval 95%) | 45.2 (24.9 to 9999999) | 45.8 (26.8 to 9999999)   | 45.2 (24.9 to 9999999) | 45.8 (26.7 to 999999999) |

|                            |   |
|----------------------------|---|
| Attachments (see zip file) | OS mITT/RAMSES Final analysis_ITT_22.07.2022_OS.bmp |
|----------------------------|---|

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title              | Log Rank Test           |
| Comparison groups                       | mITT Arm A v mITT Arm B |
| Number of subjects included in analysis | 152                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.749                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.923                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.565                   |
| upper limit                             | 1.509                   |

### Secondary: Surigcal morbidity

|                           |                    |
|---------------------------|--------------------|
| End point title           | Surigcal morbidity |
| End point description:    |                    |
| End point type            | Secondary          |
| End point timeframe:      |                    |
| upto 60 days from surgery |                    |

| End point values                     | Arm A - FLOT    | Arm B - FLOT/Ramucirumab | mITT Arm A           | mITT Arm B           |
|--------------------------------------|-----------------|--------------------------|----------------------|----------------------|
| Subject group type                   | Reporting group | Reporting group          | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 85              | 87                       | 74                   | 71                   |
| Units: subjects                      |                 |                          |                      |                      |
| Any surgical or medical complication | 30              | 39                       | 24                   | 29                   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Surgical mortality

|                 |                    |
|-----------------|--------------------|
| End point title | Surgical mortality |
|-----------------|--------------------|

End point description:

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

End point timeframe:

upto 60 days from surgery

| End point values             | Arm A - FLOT    | Arm B -<br>FLOT/Ramuciru<br>mab | mITT Arm A           | mITT Arm B           |
|------------------------------|-----------------|---------------------------------|----------------------|----------------------|
| Subject group type           | Reporting group | Reporting group                 | Subject analysis set | Subject analysis set |
| Number of subjects analysed  | 85              | 87                              | 74                   | 71                   |
| Units: Subjects              |                 |                                 |                      |                      |
| Mortality at 30 days post OP | 1               | 3                               | 1                    | 2                    |
| Mortality at 60 dyas post OP | 3               | 4                               | 3                    | 2                    |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

after patient has given written informed consent until at least 30 days after the last dose of study treatment

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 4.03 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Arm A safety population |
|-----------------------|-------------------------|

Reporting group description:

include all patients in Arm A who received at least one dose of study treatment

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Arm B safety population |
|-----------------------|-------------------------|

Reporting group description:

included all patients in Arm B who received at least one dose of study treatment

|                       |   |
|-----------------------|---|
| Reporting group title | Arm A safety population excluding GEJ I |
|-----------------------|---|

Reporting group description:

includes all patients in Arm A who received at least one dose of study treatment except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

|                       |   |
|-----------------------|---|
| Reporting group title | Arm B safety population excluding GEJ I |
|-----------------------|---|

Reporting group description:

includes all patients in Arm B who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

| Serious adverse events  | Arm A safety population | Arm B safety population | Arm A safety population excluding GEJ I |
|---|-------------------------|-------------------------|---|
| Total subjects affected by serious adverse events                   |                         |                         |   |
| subjects affected / exposed   | 45 / 90 (50.00%)        | 67 / 88 (76.14%)        | 40 / 79 (50.63%)                        |
| number of deaths (all causes)                                       | 40                      | 39                      | 34                                      |
| number of deaths resulting from adverse events                      | 4                       | 12                      | 4                                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                         |   |
| Leptomeningeal spread   |                         |                         |   |
| subjects affected / exposed   | 1 / 90 (1.11%)          | 0 / 88 (0.00%)          | 1 / 79 (1.27%)                          |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 0                   | 0 / 1                                   |
| deaths causally related to treatment / all                          | 0 / 1                   | 0 / 0                   | 0 / 1                                   |
| Vascular disorders  |                         |                         |   |
| Haematoma   |                         |                         |   |
| subjects affected / exposed   | 1 / 90 (1.11%)          | 0 / 88 (0.00%)          | 1 / 79 (1.27%)                          |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 0                   | 0 / 1                                   |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                   | 0 / 0                                   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Hypertension   |                |                |                |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 2 / 88 (2.27%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all      | 1 / 1          | 2 / 2          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension  |                |                |                |
| subjects affected / exposed                          | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Thromboembolic event                                 |                |                |                |
| subjects affected / exposed                          | 2 / 90 (2.22%) | 2 / 88 (2.27%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 1 / 1          | 0 / 0          |
| Visceral arterial ischemia                           |                |                |                |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Surgical and medical procedures                      |                |                |                |
| Abcess after surgery                                 |                |                |                |
| subjects affected / exposed                          | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Prolonged hospitalisation after surgery              |                |                |                |
| subjects affected / exposed                          | 2 / 90 (2.22%) | 0 / 88 (0.00%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Chills   |                |                |                |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 2 / 88 (2.27%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all      | 1 / 1          | 2 / 2          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Fatigue  |                |                |                |

|   |  |                |                |
|---|--|----------------|----------------|
| subjects affected / exposed                     | 1 / 90 (1.11%)                           | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1                                    | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| Fever   |  |                |                |
| subjects affected / exposed                     | 6 / 90 (6.67%)                           | 7 / 88 (7.95%) | 6 / 79 (7.59%) |
| occurrences causally related to treatment / all | 3 / 6                                    | 3 / 7          | 3 / 6          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| Flu like symptoms                               |  |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%)                           | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| Abscess on the pancreatic upper margin          |  |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%)                           | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| Collaps event                                   |  |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%)                           | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1                                    | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| obstruction of implanted port                   | Additional description: haematoma, fever |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%)                           | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| Pain exacerbation                               |  |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%)                           | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1                                    | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| Port obstruction                                |  |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%)                           | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0          | 0 / 0          |
| General physical health deterioration           |  |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 90 (2.22%) | 2 / 88 (2.27%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 1 / 2          | 1 / 2          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infusion site extravasation                     |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Multi-organ disorder                            |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Pain  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 1 / 88 (1.14%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Aspiration                                      |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchial fistula                               |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Chylothorax                                     |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Pleural effusion                                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pleural haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonitis                                     |                |                |                |
| subjects affected / exposed                     | 3 / 90 (3.33%) | 1 / 88 (1.14%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 1          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary fibrosis                              |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diaphragmatic hernia                            |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Thoracic empyema                                |                |                |                |

|   |                |                  |                |
|---|----------------|------------------|----------------|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%)   | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Psychiatric disorders                           |                |                  |                |
| Anxiety   |                |                  |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%)   | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Investigations                                  |                |                  |                |
| Neutrophil count decreased                      |                |                  |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 1 / 88 (1.14%)   | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 4 / 4          | 1 / 1            | 4 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Platelet count decreased                        |                |                  |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%)   | 0 / 79 (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          |
| Weight loss                                     |                |                  |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 88 (0.00%)   | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0            | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| White blood cell count decreased                |                |                  |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%)   | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0            | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                  |                |
| Anastomotic leak                                |                |                  |                |
| subjects affected / exposed                     | 6 / 90 (6.67%) | 10 / 88 (11.36%) | 5 / 79 (6.33%) |
| occurrences causally related to treatment / all | 0 / 7          | 3 / 10           | 0 / 5          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 3            | 0 / 1          |
| Postoperative lymphatic fistula                 |                |                  |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%)   | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1            | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| postoperative haemorrhage                       |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 2 / 88 (2.27%) | 0 / 79 (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          |
| Wound complication                              |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Circulatory dysregulation                       |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| malignant cardiac arrhythmias                   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Heart failure                                   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Palpitations                                    |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Right ventricular dysfunction                   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular fibrillation                        |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular tachycardia                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| <b>Nervous system disorders</b>                 |                |                |                |
| Dizziness                                       |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Epileptical attack                              |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Grand mal epilepsy                              |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Stroke  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Blood and lymphatic system disorders</b>     |                |                |                |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 2 / 88 (2.27%) | 0 / 79 (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          |
| <b>Eye disorders</b>                            |                |                |                |
| Extraocular muscle paresis                      |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Retinal detachment                              |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 2 / 88 (2.27%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 3 / 90 (3.33%) | 4 / 88 (4.55%) | 3 / 79 (3.80%) |
| occurrences causally related to treatment / all | 2 / 3          | 3 / 4          | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dysphagia                                       |                |                |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 5 / 88 (5.68%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 0 / 2          | 1 / 6          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Enterocolitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal stenosis                            |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophagitis                                    |                |                |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 88 (0.00%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 2 / 88 (2.27%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 2 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric perforation                             |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Gastrooesophageal reflux disease                |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Volvulus  |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ileus   |                |                |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 1 / 88 (1.14%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Jejunal stenosis                                |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Mucositis oral                                  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 3 / 90 (3.33%) | 2 / 88 (2.27%) | 3 / 79 (3.80%) |
| occurrences causally related to treatment / all | 4 / 4          | 1 / 2          | 4 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancreatitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal mucositis                                |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (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          |
| Toothache                                       |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 5 / 88 (5.68%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 2 / 6          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abcess left hepatic lobe                        |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholestasis                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 3 / 88 (3.41%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Bladder stone                                   |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract obstruction                       |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Spondylolisthesis cervical                      |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Abdominal infection                             |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 1 / 88 (1.14%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchial infection                             |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Catheter related infection                      |                |                |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 4 / 88 (4.55%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 4          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 2 / 88 (2.27%) | 0 / 79 (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          |
| Enterocolitis infectious                        |                |                |                |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 88 (0.00%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Necrotising pancreatitis                        |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Port infection                                  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholangitis transient                           |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| C-reactive protein increased                    |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 2 / 88 (2.27%) | 0 / 79 (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          |
| infection unknown origin                        |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 2 / 88 (2.27%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 3          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Laryngitis                                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 3 / 90 (3.33%) | 3 / 88 (3.41%) | 2 / 79 (2.53%) |
| occurrences causally related to treatment / all | 2 / 3          | 1 / 4          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Mucosal infection                               |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peritoneal infection                            |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 3 / 88 (3.41%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 3          | 1 / 1          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 1 / 1          |
| Skin infection                                  |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tooth infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Wound infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 88 (1.14%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Anorexia  |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 5 / 88 (5.68%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 6          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 88 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |   |  |  |
|---|---|--|--|
| <b>Serious adverse events</b>                                       | Arm B safety population excluding GEJ I |  |  |
| Total subjects affected by serious adverse events                   |   |  |  |
| subjects affected / exposed   | 54 / 72 (75.00%)                        |  |  |
| number of deaths (all causes)                                       | 30                                      |  |  |
| number of deaths resulting from adverse events                      | 6                                       |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| Leptomeningeal spread   |   |  |  |
| subjects affected / exposed   | 0 / 72 (0.00%)                          |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                   |  |  |
| Vascular disorders  |   |  |  |
| Haematoma   |   |  |  |
| subjects affected / exposed   | 0 / 72 (0.00%)                          |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                   |  |  |
| Hypertension  |   |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 2 / 72 (2.78%) |  |  |
| occurrences causally related to treatment / all      | 2 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hypotension  |                |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Thromboembolic event                                 |                |  |  |
| subjects affected / exposed                          | 2 / 72 (2.78%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2          |  |  |
| deaths causally related to treatment / all           | 1 / 1          |  |  |
| Visceral arterial ischemia                           |                |  |  |
| subjects affected / exposed                          | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgical and medical procedures                      |                |  |  |
| Abcess after surgery                                 |                |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Prolonged hospitalisation after surgery              |                |  |  |
| subjects affected / exposed                          | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Chills   |                |  |  |
| subjects affected / exposed                          | 2 / 72 (2.78%) |  |  |
| occurrences causally related to treatment / all      | 2 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fatigue  |                |  |  |
| subjects affected / exposed                          | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|   |  |  |  |  |
|---|--|--|--|--|
| Fever   |  |  |  |  |
| subjects affected / exposed                     | 7 / 72 (9.72%)                           |  |  |  |
| occurrences causally related to treatment / all | 3 / 7                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| Flu like symptoms                               |  |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%)                           |  |  |  |
| occurrences causally related to treatment / all | 0 / 0                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| Abscess on the pancreatic upper margin          |  |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)                           |  |  |  |
| occurrences causally related to treatment / all | 0 / 1                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| Collaps event                                   |  |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%)                           |  |  |  |
| occurrences causally related to treatment / all | 0 / 0                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| obstruction of implanted port                   | Additional description: haematoma, fever |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)                           |  |  |  |
| occurrences causally related to treatment / all | 0 / 1                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| Pain exacerbation                               |  |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%)                           |  |  |  |
| occurrences causally related to treatment / all | 0 / 0                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| Port obstruction                                |  |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)                           |  |  |  |
| occurrences causally related to treatment / all | 0 / 1                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| General physical health deterioration           |  |  |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%)                           |  |  |  |
| occurrences causally related to treatment / all | 1 / 2                                    |  |  |  |
| deaths causally related to treatment / all      | 0 / 0                                    |  |  |  |
| Infusion site extravasation                     |  |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Multi-organ disorder                            |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Pain  |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Aspiration                                      |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bronchial fistula                               |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Chylothorax                                     |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural haemorrhage                             |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonitis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumothorax                                    |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory failure                             |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary fibrosis                              |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diaphragmatic hernia                            |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thoracic empyema                                |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Anxiety   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                           | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |
| <b>Investigations</b>                                 |                |  |  |
| Neutrophil count decreased                            |                |  |  |
| subjects affected / exposed                           | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all       | 1 / 1          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |
| Platelet count decreased                              |                |  |  |
| subjects affected / exposed                           | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all       | 2 / 2          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |
| Weight loss   |                |  |  |
| subjects affected / exposed                           | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |
| White blood cell count decreased                      |                |  |  |
| subjects affected / exposed                           | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |
| <b>Injury, poisoning and procedural complications</b> |                |  |  |
| Anastomotic leak                                      |                |  |  |
| subjects affected / exposed                           | 6 / 72 (8.33%) |  |  |
| occurrences causally related to treatment / all       | 1 / 6          |  |  |
| deaths causally related to treatment / all            | 0 / 1          |  |  |
| Postoperative lymphatic fistula                       |                |  |  |
| subjects affected / exposed                           | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |
| postoperative haemorrhage                             |                |  |  |
| subjects affected / exposed                           | 2 / 72 (2.78%) |  |  |
| occurrences causally related to treatment / all       | 0 / 2          |  |  |
| deaths causally related to treatment / all            | 0 / 0          |  |  |

|   |                                  |  |  |
|---|----------------------------------|--|--|
| Wound complication<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all            | 0 / 72 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Cardiac disorders   |                                  |  |  |
| Circulatory dysregulation<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all     | 1 / 72 (1.39%)<br>1 / 1<br>0 / 0 |  |  |
| malignant cardiac arrhythmias<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 72 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Heart failure<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | 0 / 72 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Palpitations<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | 0 / 72 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Right ventricular dysfunction<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 72 (1.39%)<br>0 / 1<br>0 / 0 |  |  |
| Ventricular fibrillation<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all      | 0 / 72 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Ventricular tachycardia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all       | 0 / 72 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Nervous system disorders  |                                  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Dizziness                                       |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Epileptical attack                              |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Grand mal epilepsy                              |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Stroke  |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Syncope   |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Febrile neutropenia                             |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Extraocular muscle paresis                      |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Retinal detachment                              |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 3 / 72 (4.17%) |  |  |
| occurrences causally related to treatment / all | 2 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dysphagia                                       |                |  |  |
| subjects affected / exposed                     | 5 / 72 (6.94%) |  |  |
| occurrences causally related to treatment / all | 1 / 6          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Enterocolitis                                   |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oesophageal stenosis                            |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oesophagitis                                    |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastric haemorrhage                             |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastric perforation                             |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |
| Gastrooesophageal reflux disease                |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastroenteritis                                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Volvulus  |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Ileus   |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Jejunal stenosis                                |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower gastrointestinal haemorrhage              |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Mucositis oral                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Nausea  |                |  |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pancreatitis                                    |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Rectal mucositis                                |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Toothache                                       |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper gastrointestinal haemorrhage              |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 4 / 72 (5.56%) |  |  |
| occurrences causally related to treatment / all | 2 / 5          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholecystitis                                   |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abcess left hepatic lobe                        |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholestasis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Acute kidney injury                             |                |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Bladder stone                                   |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract obstruction                       |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Spondylolisthesis cervical                      |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Abdominal infection                             |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bronchial infection                             |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Catheter related infection                      |                |  |  |
| subjects affected / exposed                     | 3 / 72 (4.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Device related infection                        |                |  |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Enterocolitis infectious                        |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Necrotising pancreatitis                        |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Port infection                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cholangitis transient                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| C-reactive protein increased                    |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| infection unknown origin                        |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Laryngitis                                      |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lung infection                                  |                |  |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Mucosal infection                               |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peritoneal infection                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis  |                |  |  |  |
| subjects affected / exposed                     | 3 / 72 (4.17%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Skin infection                                  |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tooth infection                                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Upper respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Urinary tract infection                         |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Wound infection                                 |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Anorexia  |                |  |  |
| subjects affected / exposed                     | 3 / 72 (4.17%) |  |  |
| occurrences causally related to treatment / all | 1 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 0 / 72 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| Non-serious adverse events                            | Arm A safety population | Arm B safety population | Arm A safety population excluding GEJ I |
|---|-------------------------|-------------------------|---|
| Total subjects affected by non-serious adverse events |                         |                         |   |
| subjects affected / exposed                           | 88 / 90 (97.78%)        | 88 / 88 (100.00%)       | 77 / 79 (97.47%)                        |
| Vascular disorders                                    |                         |                         |   |
| Hypertension  |                         |                         |   |
| subjects affected / exposed                           | 4 / 90 (4.44%)          | 11 / 88 (12.50%)        | 4 / 79 (5.06%)                          |
| occurrences (all)                                     | 4                       | 16                      | 4                                       |
| Thromboembolic event                                  |                         |                         |   |
| subjects affected / exposed                           | 6 / 90 (6.67%)          | 6 / 88 (6.82%)          | 5 / 79 (6.33%)                          |
| occurrences (all)                                     | 6                       | 8                       | 5                                       |
| General disorders and administration site conditions  |                         |                         |   |
| Chills  |                         |                         |   |
| subjects affected / exposed                           | 5 / 90 (5.56%)          | 8 / 88 (9.09%)          | 5 / 79 (6.33%)                          |
| occurrences (all)                                     | 5                       | 8                       | 5                                       |
| Edema limbs   |                         |                         |   |
| subjects affected / exposed                           | 6 / 90 (6.67%)          | 16 / 88 (18.18%)        | 4 / 79 (5.06%)                          |
| occurrences (all)                                     | 6                       | 25                      | 4                                       |
| Fatigue   |                         |                         |   |

|  |                         |                         |                        |
|--|-------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 52 / 90 (57.78%)<br>111 | 48 / 88 (54.55%)<br>109 | 44 / 79 (55.70%)<br>87 |
| Fever<br>subjects affected / exposed<br>occurrences (all)  | 23 / 90 (25.56%)<br>28  | 24 / 88 (27.27%)<br>29  | 19 / 79 (24.05%)<br>24 |
| Pain<br>subjects affected / exposed<br>occurrences (all)   | 21 / 90 (23.33%)<br>34  | 30 / 88 (34.09%)<br>52  | 15 / 79 (18.99%)<br>26 |
| Immune system disorders<br>Allergic reaction<br>subjects affected / exposed<br>occurrences (all)             | 4 / 90 (4.44%)<br>4     | 7 / 88 (7.95%)<br>9     | 4 / 79 (5.06%)<br>4    |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 8 / 90 (8.89%)<br>8     | 7 / 88 (7.95%)<br>8     | 4 / 79 (5.06%)<br>4    |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 4 / 90 (4.44%)<br>6     | 8 / 88 (9.09%)<br>14    | 2 / 79 (2.53%)<br>2    |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 8 / 90 (8.89%)<br>9     | 20 / 88 (22.73%)<br>24  | 5 / 79 (6.33%)<br>5    |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)   | 6 / 90 (6.67%)<br>7     | 18 / 88 (20.45%)<br>24  | 2 / 79 (2.53%)<br>2    |
| Pneumonitis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 90 (3.33%)<br>3     | 2 / 88 (2.27%)<br>2     | 3 / 79 (3.80%)<br>3    |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 90 (4.44%)<br>5     | 5 / 88 (5.68%)<br>7     | 2 / 79 (2.53%)<br>2    |
| Investigations<br>Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)             | 36 / 90 (40.00%)<br>72  | 44 / 88 (50.00%)<br>84  | 28 / 79 (35.44%)<br>57 |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)   | 6 / 90 (6.67%)<br>9    | 9 / 88 (10.23%)<br>13  | 4 / 79 (5.06%)<br>7    |
| Weight loss<br>subjects affected / exposed<br>occurrences (all)  | 16 / 90 (17.78%)<br>18 | 17 / 88 (19.32%)<br>23 | 15 / 79 (18.99%)<br>17 |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                                     | 36 / 90 (40.00%)<br>87 | 33 / 88 (37.50%)<br>53 | 29 / 79 (36.71%)<br>74 |
| Injury, poisoning and procedural complications<br>Wound complication<br>subjects affected / exposed<br>occurrences (all) | 1 / 90 (1.11%)<br>1    | 5 / 88 (5.68%)<br>7    | 1 / 79 (1.27%)<br>1    |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                                | 4 / 90 (4.44%)<br>5    | 10 / 88 (11.36%)<br>12 | 4 / 79 (5.06%)<br>5    |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)  | 14 / 90 (15.56%)<br>15 | 12 / 88 (13.64%)<br>15 | 11 / 79 (13.92%)<br>12 |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 5 / 90 (5.56%)<br>5    | 8 / 88 (9.09%)<br>10   | 3 / 79 (3.80%)<br>3    |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)   | 21 / 90 (23.33%)<br>40 | 22 / 88 (25.00%)<br>46 | 18 / 79 (22.78%)<br>34 |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)  | 36 / 90 (40.00%)<br>71 | 37 / 88 (42.05%)<br>74 | 29 / 79 (36.71%)<br>55 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                      | 20 / 90 (22.22%)<br>25 | 10 / 88 (11.36%)<br>11 | 19 / 79 (24.05%)<br>19 |
| Ear and labyrinth disorders<br>Vertigo   |                        |                        |                        |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 5 / 90 (5.56%)<br>9 | 3 / 88 (3.41%)<br>4 | 4 / 79 (5.06%)<br>7 |
| Gastrointestinal disorders                       |                     |                     |                     |
| Abdominal pain                                   |                     |                     |                     |
| subjects affected / exposed                      | 17 / 90 (18.89%)    | 16 / 88 (18.18%)    | 14 / 79 (17.72%)    |
| occurrences (all)                                | 23                  | 24                  | 22                  |
| Ascites  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 90 (0.00%)      | 5 / 88 (5.68%)      | 0 / 79 (0.00%)      |
| occurrences (all)                                | 0                   | 5                   | 0                   |
| Constipation                                     |                     |                     |                     |
| subjects affected / exposed                      | 19 / 90 (21.11%)    | 19 / 88 (21.59%)    | 15 / 79 (18.99%)    |
| occurrences (all)                                | 20                  | 22                  | 16                  |
| Diarrhoea  |                     |                     |                     |
| subjects affected / exposed                      | 58 / 90 (64.44%)    | 52 / 88 (59.09%)    | 52 / 79 (65.82%)    |
| occurrences (all)                                | 121                 | 152                 | 99                  |
| Dyspepsia  |                     |                     |                     |
| subjects affected / exposed                      | 5 / 90 (5.56%)      | 3 / 88 (3.41%)      | 4 / 79 (5.06%)      |
| occurrences (all)                                | 5                   | 3                   | 4                   |
| Dysphagia  |                     |                     |                     |
| subjects affected / exposed                      | 9 / 90 (10.00%)     | 7 / 88 (7.95%)      | 10 / 79 (12.66%)    |
| occurrences (all)                                | 11                  | 10                  | 10                  |
| Gastrooesophageal reflux disease                 |                     |                     |                     |
| subjects affected / exposed                      | 5 / 90 (5.56%)      | 6 / 88 (6.82%)      | 5 / 79 (6.33%)      |
| occurrences (all)                                | 8                   | 7                   | 7                   |
| Mucositis oral                                   |                     |                     |                     |
| subjects affected / exposed                      | 27 / 90 (30.00%)    | 29 / 88 (32.95%)    | 25 / 79 (31.65%)    |
| occurrences (all)                                | 45                  | 50                  | 36                  |
| Nausea   |                     |                     |                     |
| subjects affected / exposed                      | 55 / 90 (61.11%)    | 56 / 88 (63.64%)    | 46 / 79 (58.23%)    |
| occurrences (all)                                | 128                 | 142                 | 107                 |
| Vomiting   |                     |                     |                     |
| subjects affected / exposed                      | 22 / 90 (24.44%)    | 33 / 88 (37.50%)    | 15 / 79 (18.99%)    |
| occurrences (all)                                | 39                  | 65                  | 28                  |
| Skin and subcutaneous tissue disorders           |                     |                     |                     |
| Alopecia   |                     |                     |                     |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 47 / 90 (52.22%)<br>57 | 39 / 88 (44.32%)<br>49 | 36 / 79 (45.57%)<br>43 |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)  | 5 / 90 (5.56%)<br>5    | 4 / 88 (4.55%)<br>4    | 5 / 79 (6.33%)<br>5    |
| Palmar-plantar erythrodysaesthesia<br>syndrome<br>subjects affected / exposed<br>occurrences (all)            | 18 / 90 (20.00%)<br>24 | 14 / 88 (15.91%)<br>24 | 13 / 79 (16.46%)<br>17 |
| Rash acneiform<br>subjects affected / exposed<br>occurrences (all)  | 4 / 90 (4.44%)<br>4    | 6 / 88 (6.82%)<br>6    | 4 / 79 (5.06%)<br>4    |
| Renal and urinary disorders<br>Proteinuria<br>subjects affected / exposed<br>occurrences (all)                | 0 / 90 (0.00%)<br>0    | 8 / 88 (9.09%)<br>16   | 0 / 79 (0.00%)<br>0    |
| Infections and infestations<br>Catheter related infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 90 (1.11%)<br>1    | 2 / 88 (2.27%)<br>2    | 0 / 79 (0.00%)<br>0    |
| Device related infection<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 90 (1.11%)<br>1    | 4 / 88 (4.55%)<br>4    | 1 / 79 (1.27%)<br>1    |
| Lung infection<br>subjects affected / exposed<br>occurrences (all)  | 3 / 90 (3.33%)<br>3    | 2 / 88 (2.27%)<br>2    | 2 / 79 (2.53%)<br>2    |
| Sepsis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 90 (2.22%)<br>2    | 3 / 88 (3.41%)<br>3    | 2 / 79 (2.53%)<br>2    |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 90 (2.22%)<br>2    | 7 / 88 (7.95%)<br>8    | 0 / 79 (0.00%)<br>0    |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all)            | 21 / 90 (23.33%)<br>27 | 13 / 88 (14.77%)<br>28 | 19 / 79 (24.05%)<br>19 |

| <b>Non-serious adverse events</b>                     | Arm B safety population excluding GEJ I |  |  |
|---|---|--|--|
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 72 / 72 (100.00%)                       |  |  |
| Vascular disorders                                    |   |  |  |
| Hypertension  |   |  |  |
| subjects affected / exposed                           | 11 / 72 (15.28%)                        |  |  |
| occurrences (all)                                     | 16                                      |  |  |
| Thromboembolic event                                  |   |  |  |
| subjects affected / exposed                           | 6 / 72 (8.33%)                          |  |  |
| occurrences (all)                                     | 8                                       |  |  |
| General disorders and administration site conditions  |   |  |  |
| Chills  |   |  |  |
| subjects affected / exposed                           | 8 / 72 (11.11%)                         |  |  |
| occurrences (all)                                     | 8                                       |  |  |
| Edema limbs   |   |  |  |
| subjects affected / exposed                           | 15 / 72 (20.83%)                        |  |  |
| occurrences (all)                                     | 24                                      |  |  |
| Fatigue   |   |  |  |
| subjects affected / exposed                           | 42 / 72 (58.33%)                        |  |  |
| occurrences (all)                                     | 96                                      |  |  |
| Fever   |   |  |  |
| subjects affected / exposed                           | 20 / 72 (27.78%)                        |  |  |
| occurrences (all)                                     | 25                                      |  |  |
| Pain  |   |  |  |
| subjects affected / exposed                           | 27 / 72 (37.50%)                        |  |  |
| occurrences (all)                                     | 46                                      |  |  |
| Immune system disorders                               |   |  |  |
| Allergic reaction                                     |   |  |  |
| subjects affected / exposed                           | 5 / 72 (6.94%)                          |  |  |
| occurrences (all)                                     | 7                                       |  |  |
| Respiratory, thoracic and mediastinal disorders       |   |  |  |
| Cough   |   |  |  |
| subjects affected / exposed                           | 5 / 72 (6.94%)                          |  |  |
| occurrences (all)                                     | 6                                       |  |  |
| Dyspnoea  |   |  |  |

|  |   |  |  |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleural effusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pneumonitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>6 / 72 (8.33%)</p> <p>6</p> <p>15 / 72 (20.83%)</p> <p>19</p> <p>13 / 72 (18.06%)</p> <p>20</p> <p>1 / 72 (1.39%)</p> <p>1</p>     |  |  |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 72 (2.78%)</p> <p>4</p>  |  |  |
| <p>Investigations</p> <p>Neutrophil count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight loss</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>34 / 72 (47.22%)</p> <p>61</p> <p>7 / 72 (9.72%)</p> <p>12</p> <p>14 / 72 (19.44%)</p> <p>20</p> <p>25 / 72 (34.72%)</p> <p>40</p> |  |  |
| <p>Injury, poisoning and procedural complications</p> <p>Wound complication</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>5 / 72 (6.94%)</p> <p>7</p>  |  |  |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>9 / 72 (12.50%)</p> <p>12</p>  |  |  |

|   |                         |  |  |
|---|-------------------------|--|--|
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                       | 12 / 72 (16.67%)<br>15  |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 7 / 72 (9.72%)<br>8     |  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                    | 15 / 72 (20.83%)<br>38  |  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                   | 29 / 72 (40.28%)<br>66  |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 10 / 72 (13.89%)<br>10  |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)          | 2 / 72 (2.78%)<br>3     |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)    | 15 / 72 (20.83%)<br>24  |  |  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)   | 4 / 72 (5.56%)<br>0     |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                    | 14 / 72 (19.44%)<br>17  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                       | 42 / 72 (58.33%)<br>128 |  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 72 (2.78%)<br>2     |  |  |
| Dysphagia   |                         |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                 | 8 / 72 (11.11%)  |  |  |
| occurrences (all)                           | 9                |  |  |
| Gastrooesophageal reflux disease            |                  |  |  |
| subjects affected / exposed                 | 5 / 72 (6.94%)   |  |  |
| occurrences (all)                           | 6                |  |  |
| Mucositis oral                              |                  |  |  |
| subjects affected / exposed                 | 25 / 72 (34.72%) |  |  |
| occurrences (all)                           | 47               |  |  |
| Nausea                                      |                  |  |  |
| subjects affected / exposed                 | 51 / 72 (70.83%) |  |  |
| occurrences (all)                           | 132              |  |  |
| Vomiting                                    |                  |  |  |
| subjects affected / exposed                 | 34 / 72 (47.22%) |  |  |
| occurrences (all)                           | 61               |  |  |
| Skin and subcutaneous tissue disorders      |                  |  |  |
| Alopecia                                    |                  |  |  |
| subjects affected / exposed                 | 33 / 72 (45.83%) |  |  |
| occurrences (all)                           | 43               |  |  |
| Dry skin                                    |                  |  |  |
| subjects affected / exposed                 | 2 / 72 (2.78%)   |  |  |
| occurrences (all)                           | 2                |  |  |
| Palmar-plantar erythrodysaesthesia syndrome |                  |  |  |
| subjects affected / exposed                 | 12 / 72 (16.67%) |  |  |
| occurrences (all)                           | 22               |  |  |
| Rash acneiform                              |                  |  |  |
| subjects affected / exposed                 | 5 / 72 (6.94%)   |  |  |
| occurrences (all)                           | 5                |  |  |
| Renal and urinary disorders                 |                  |  |  |
| Proteinuria                                 |                  |  |  |
| subjects affected / exposed                 | 8 / 72 (11.11%)  |  |  |
| occurrences (all)                           | 16               |  |  |
| Infections and infestations                 |                  |  |  |
| Catheter related infection                  |                  |  |  |
| subjects affected / exposed                 | 1 / 72 (1.39%)   |  |  |
| occurrences (all)                           | 1                |  |  |
| Device related infection                    |                  |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 4 / 72 (5.56%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Lung infection                     |                  |  |  |
| subjects affected / exposed        | 0 / 72 (0.00%)   |  |  |
| occurrences (all)                  | 0                |  |  |
| Sepsis                             |                  |  |  |
| subjects affected / exposed        | 1 / 72 (1.39%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 2 / 72 (2.78%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Anorexia                           |                  |  |  |
| subjects affected / exposed        | 12 / 72 (16.67%) |  |  |
| occurrences (all)                  | 12               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 November 2017 | <ul style="list-style-type: none"><li>- Patients with esophageal cancer and those with adenocarcinoma of GEJ type I and all patients who are planned to have transthoracic esophagectomy must no longer be included</li><li>- Patients with severe, especially vascular, concomitant diseases (e.g., pAVK, chronic nicotine and/or previous alcohol abuse) are no longer included</li><li>- Handling instructions for patients with GEJ type I and II who were already enrolled have been added</li></ul> |
| 08 March 2018    | <ol style="list-style-type: none"><li>1) After exclusion of AEG/GEJ type I tumors in the 1st amendment of the study, it was decided to replace the 28 affected patients with an enrollment of 30 additional patients, increasing the total sample size to 180 patients</li><li>2) Extension of the study to Italy</li></ol>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date            | Interruption   | Restart date     |
|-----------------|--|------------------|
| 27 October 2017 | <p>An interim safety analysis, examining six deaths which occurred during the study after nearly 40 patients in each arm underwent surgery, revealed that almost all of these died from anastomotic leakage (in some cases months after surgery), received FLOT/ramucirumab, had GEJ type I adenocarcinomas undergoing transthoracic esophagectomy and had in mean three relevant comorbidities predominantly cardiovascular disease like peripheral arterial occlusive disease (PAOD) and chronic heart failure as well as diabetes mellitus, chronic nicotine and/or previous alcohol abuse.</p> <p>Based on these findings, the study protocol was amended in November 2017 to exclude patients with potential increased risk including patients with GEJ type I and planned transthoracic esophagectomy from further enrolment</p> | 30 November 2017 |

Notes:

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36883420>