



## Clinical trial results:

### A Multicenter, Single arm, Open Label Clinical Trial to Evaluate the Safety and Health-Related Quality of Life of Aflibercept in Patients with Metastatic Colorectal Cancer (mCRC) Previously Treated with an Oxaliplatin-Containing Regimen

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2011-005724-17                      |
| Trial protocol           | BE SE DK FI DE NL IT ES IE CZ SI HU |
| Global end of trial date | 31 January 2017                     |

#### Results information

|                                |                                                                                                                                           |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                                              |
| This version publication date  | 22 April 2018                                                                                                                             |
| First version publication date | 15 February 2018                                                                                                                          |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Update to baseline characteristics and endpoint description |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | AFLIBC06097 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT01571284     |
| WHO universal trial number (UTN)   | U1111-1125-8949 |

Notes:

#### Sponsors

|                              |                                                                                          |
|------------------------------|------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Sanofi aventis recherche & développement                                                 |
| Sponsor organisation address | 1 avenue Pierre Brossolette , Chilly-Mazarin, France, 91380                              |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 14 March 2017   |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 January 2017 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To provide mCRC subjects (similar to the subjects evaluated in the VELOUR [EFC10262] phase III trial) and investigators with access to aflibercept, prior to its marketing authorization and/or commercial availability and to document the aflibercept overall safety in this subject population.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 30 May 2012 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Brazil: 41             |
| Country: Number of subjects enrolled | Canada: 49             |
| Country: Number of subjects enrolled | Chile: 1               |
| Country: Number of subjects enrolled | Israel: 14             |
| Country: Number of subjects enrolled | Lebanon: 7             |
| Country: Number of subjects enrolled | Mexico: 9              |
| Country: Number of subjects enrolled | Norway: 3              |
| Country: Number of subjects enrolled | Puerto Rico: 2         |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | Thailand: 111          |
| Country: Number of subjects enrolled | Turkey: 40             |
| Country: Number of subjects enrolled | United Kingdom: 54     |
| Country: Number of subjects enrolled | United States: 4       |
| Country: Number of subjects enrolled | Netherlands: 15        |
| Country: Number of subjects enrolled | Spain: 77              |
| Country: Number of subjects enrolled | Sweden: 5              |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 32        |
| Country: Number of subjects enrolled | Czech Republic: 20 |
| Country: Number of subjects enrolled | Denmark: 14        |
| Country: Number of subjects enrolled | Finland: 3         |
| Country: Number of subjects enrolled | Germany: 42        |
| Country: Number of subjects enrolled | Ireland: 6         |
| Country: Number of subjects enrolled | Italy: 200         |
| Worldwide total number of subjects   | 779                |
| EEA total number of subjects         | 471                |

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)                      | 475 |
| From 65 to 84 years                       | 303 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 151 sites in 23 countries. A total of 798 subjects were screened between 30 May 2012 and 03 January 2015, out of which 781 subjects were enrolled and 779 subjects were treated.

### Pre-assignment

Screening details:

Subjects enrolled in the study to assess the safety of Aflibercept in subjects treated with a combination of Aflibercept with FOLFIRI regimen (Irinotecan, Leucovorin and 5-Fluorouracil [5-FU]). 403 subjects with disease progression (DP) and 209 with adverse events were considered as completed.

### Period 1

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

### Arms

|           |                                                       |
|-----------|-------------------------------------------------------|
| Arm title | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |
|-----------|-------------------------------------------------------|

Arm description:

Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m<sup>2</sup> IV infusion over 90 minutes and Leucovorin 400 mg/m<sup>2</sup> IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m<sup>2</sup> IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m<sup>2</sup> continuous IV infusion over 46 hours on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment.

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Aflibercept                     |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Aflibercept (referred to also as VEGF-Trap or AVE0005) was to be provided as a 25 mg/mL concentrate solution for infusion.

| Number of subjects in period 1 | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |
|--------------------------------|-------------------------------------------------------|
| Started                        | 779                                                   |
| Safety population              | 779                                                   |
| Completed                      | 612                                                   |
| Not completed                  | 167                                                   |
| Other than specified above     | 80                                                    |
| Subject's decision             | 84                                                    |
| Lost to follow-up              | 3                                                     |



## Baseline characteristics

### Reporting groups

|                       |                                                       |
|-----------------------|-------------------------------------------------------|
| Reporting group title | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |
|-----------------------|-------------------------------------------------------|

Reporting group description:

Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m<sup>2</sup> IV infusion over 90 minutes and Leucovorin 400 mg/m<sup>2</sup> IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m<sup>2</sup> IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m<sup>2</sup> continuous IV infusion over 46 hours on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment.

| Reporting group values | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) | Total |  |
|------------------------|-------------------------------------------------------|-------|--|
| Number of subjects     | 779                                                   | 779   |  |
| Age categorical        |                                                       |       |  |
| Units: Subjects        |                                                       |       |  |

|                                                                                                                        |        |     |  |
|------------------------------------------------------------------------------------------------------------------------|--------|-----|--|
| Age continuous                                                                                                         |        |     |  |
| Here Number analyzed = subjects analyzed for specified categories                                                      |        |     |  |
| Units: years                                                                                                           |        |     |  |
| arithmetic mean                                                                                                        | 60.3   |     |  |
| standard deviation                                                                                                     | ± 11.0 | -   |  |
| Gender categorical                                                                                                     |        |     |  |
| Units: Subjects                                                                                                        |        |     |  |
| Female                                                                                                                 | 314    | 314 |  |
| Male                                                                                                                   | 465    | 465 |  |
| Race/Ethnicity, Customized                                                                                             |        |     |  |
| Units: Subjects                                                                                                        |        |     |  |
| White                                                                                                                  | 631    | 631 |  |
| Black or African                                                                                                       | 8      | 8   |  |
| American Asian                                                                                                         | 121    | 121 |  |
| Other                                                                                                                  | 19     | 19  |  |
| Location of Primary Tumor                                                                                              |        |     |  |
| Units: Subjects                                                                                                        |        |     |  |
| Colon                                                                                                                  | 406    | 406 |  |
| Recto sigmoid                                                                                                          | 171    | 171 |  |
| Rectum                                                                                                                 | 200    | 200 |  |
| Other                                                                                                                  | 2      | 2   |  |
| Histology                                                                                                              |        |     |  |
| Units: Subjects                                                                                                        |        |     |  |
| Adenocarcinoma                                                                                                         | 778    | 778 |  |
| Other                                                                                                                  | 1      | 1   |  |
| Any Relevant Medical/Surgical History                                                                                  |        |     |  |
| Any relevant medical/surgical history including detailed cardiovascular risk factors and prior vascular events if any. |        |     |  |
| Units: Subjects                                                                                                        |        |     |  |
| Any Relevant Medical/Surgical History                                                                                  | 640    | 640 |  |
| Unknown                                                                                                                | 139    | 139 |  |
| History of Thrombovascular Event                                                                                       |        |     |  |

|                                                                                                                                                                                                                                                                                                                                        |        |     |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----|--|
| and/or Presence of Cardiovascular Risk Factor                                                                                                                                                                                                                                                                                          |        |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                        |        |     |  |
| Thrombovascular Event and/or Presence of CV Risk                                                                                                                                                                                                                                                                                       | 424    | 424 |  |
| Unknown                                                                                                                                                                                                                                                                                                                                | 355    | 355 |  |
| Location of Primary Tumor                                                                                                                                                                                                                                                                                                              |        |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                        |        |     |  |
| Colon                                                                                                                                                                                                                                                                                                                                  | 406    | 406 |  |
| Recto sigmoid                                                                                                                                                                                                                                                                                                                          | 171    | 171 |  |
| Rectum                                                                                                                                                                                                                                                                                                                                 | 200    | 200 |  |
| Other                                                                                                                                                                                                                                                                                                                                  | 2      | 2   |  |
| Histology                                                                                                                                                                                                                                                                                                                              |        |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                        |        |     |  |
| Adenocarcinoma                                                                                                                                                                                                                                                                                                                         | 778    | 778 |  |
| Other                                                                                                                                                                                                                                                                                                                                  | 1      | 1   |  |
| Organs with Metastases at Baseline                                                                                                                                                                                                                                                                                                     |        |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                        |        |     |  |
| = 1                                                                                                                                                                                                                                                                                                                                    | 358    | 358 |  |
| >1                                                                                                                                                                                                                                                                                                                                     | 421    | 421 |  |
| Eastern Cooperative Oncology Group Performance Status (ECOG PS)                                                                                                                                                                                                                                                                        |        |     |  |
| Measure Description: ECOG PS is used to assess how the disease affects the daily living abilities of the subject. It ranges on the scale from 0-5 (0= normal activity; 1= symptoms but ambulatory; 2= in bed for less than (<) 50 percent (%) of the time; 3= in bed for greater than (>) 50% of the time; 4= 100% bedridden; 5= dead. |        |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                        |        |     |  |
| ECOG PS = 0                                                                                                                                                                                                                                                                                                                            | 484    | 484 |  |
| ECOG PS = 1                                                                                                                                                                                                                                                                                                                            | 292    | 292 |  |
| Missing                                                                                                                                                                                                                                                                                                                                | 3      | 3   |  |
| Body Surface Area (BSA)                                                                                                                                                                                                                                                                                                                |        |     |  |
| Units: m <sup>2</sup>                                                                                                                                                                                                                                                                                                                  |        |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                        | 1.80   |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                     | ± 0.23 | -   |  |
| Systolic Blood Pressure                                                                                                                                                                                                                                                                                                                |        |     |  |
| Data for Systolic Blood Pressure is reported for a total of 776 subjects.                                                                                                                                                                                                                                                              |        |     |  |
| Units: mmHg                                                                                                                                                                                                                                                                                                                            |        |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                        | 126.4  |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                     | ± 13.4 | -   |  |
| Diastolic Blood Pressure                                                                                                                                                                                                                                                                                                               |        |     |  |
| Data for Diastolic Blood Pressure is reported for a total of 776 subjects.                                                                                                                                                                                                                                                             |        |     |  |
| Units: mmHg                                                                                                                                                                                                                                                                                                                            |        |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                        | 76.4   |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                     | ± 9.0  | -   |  |
| Time From Initial Histological Diagnosis till Baseline Visit                                                                                                                                                                                                                                                                           |        |     |  |
| Units: Months                                                                                                                                                                                                                                                                                                                          |        |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                        | 19.1   |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                     | ± 17.2 | -   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                       |
| Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m <sup>2</sup> IV infusion over 90 minutes and Leucovorin 400 mg/m <sup>2</sup> IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m <sup>2</sup> IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m <sup>2</sup> continuous IV infusion over 46 hours on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment. |                                                       |

### Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

|                 |                                                                                  |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) <sup>[1]</sup> |
|-----------------|----------------------------------------------------------------------------------|

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an adverse event (AE) without regard to possibility of causal relationship with this treatment. A serious adverse event: Any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Version 4.03 was used to assess severity (Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling) of AEs. Safety population defined as the subjects who signed the informed consent form and received at least one dose of study treatment.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

| End point values                               | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
|------------------------------------------------|-------------------------------------------------------|--|--|--|
| Subject group type                             | Reporting group                                       |  |  |  |
| Number of subjects analysed                    | 779                                                   |  |  |  |
| Units: Subjects                                |                                                       |  |  |  |
| Any TEAE (All Grades)                          | 769                                                   |  |  |  |
| Any TEAEs (Grades 3-4)                         | 609                                                   |  |  |  |
| Any serious TEAE                               | 272                                                   |  |  |  |
| Any serious related TEAE                       | 159                                                   |  |  |  |
| Any TEAE leading to death                      | 47                                                    |  |  |  |
| Any TEAE (permanent treatment discontinuation) | 208                                                   |  |  |  |
| Any TEAE (premature treatment discontinuation) | 104                                                   |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Abnormal Hematological Parameters During Treatment

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Abnormal Hematological Parameters During Treatment <sup>[2]</sup> |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

Abnormal hematological parameters included: anaemia, thrombocytopenia, leukopenia and neutropenia. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4 as per NCI CTCAE (Version 4.03), where Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here, 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                                       |                                                       |  |  |  |
|---------------------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>               | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type                    | Reporting group                                       |  |  |  |
| Number of subjects analysed           | 779                                                   |  |  |  |
| Units: Subjects                       |                                                       |  |  |  |
| Anaemia: All Grades (n= 744)          | 535                                                   |  |  |  |
| Anaemia: Grades 3-4 (n= 744)          | 14                                                    |  |  |  |
| Thrombocytopenia: All Grades (n= 745) | 293                                                   |  |  |  |
| Thrombocytopenia: Grades 3-4 (n= 745) | 13                                                    |  |  |  |
| Leukopenia: All Grades (n =745)       | 532                                                   |  |  |  |
| Leukopenia: Grades 3-4 (n =745)       | 72                                                    |  |  |  |
| Neutropenia: All Grades (n= 744)      | 450                                                   |  |  |  |
| Neutropenia: Grades 3-4 (n= 744)      | 227                                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With International Normalized Ratio (INR)

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Number of Subjects With International Normalized Ratio |
|-----------------|--------------------------------------------------------|

End point description:

The INR is a derived measure of the prothrombin time. The INR is the ratio of a subject's prothrombin time to a normal control sample. Normal range (without anti coagulation therapy): 0.8-1.2; Targeted range (with anti coagulation therapy) 2.0-3.0. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

| End point values            | Aflibercept +<br>FOLFIRI<br>(Irinotecan, 5-<br>FU &<br>Leucovorin) |  |  |  |
|-----------------------------|--------------------------------------------------------------------|--|--|--|
| Subject group type          | Reporting group                                                    |  |  |  |
| Number of subjects analysed | 779                                                                |  |  |  |
| Units: subjects             |                                                                    |  |  |  |
| INR<1.5 (n= 110)            | 106                                                                |  |  |  |
| INR>=1.5 to <3 (n =110)     | 0                                                                  |  |  |  |
| INR>=3 to <5 (n =110)       | 2                                                                  |  |  |  |
| INR>=5 (n =110)             | 2                                                                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Abnormal Electrolytes Parameters

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Number of Subjects With Abnormal Electrolytes Parameters <sup>[4]</sup> |
|-----------------|-------------------------------------------------------------------------|

End point description:

Abnormal electrolytes parameters included: hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypokalemia, and hyperkalemia. Number of subjects with each of these parameters were analyzed by grades ( All Grades and Grades 3-4 as per NCI CTCAE Version 4.03, where Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

| End point values                   | Aflibercept +<br>FOLFIRI<br>(Irinotecan, 5-<br>FU &<br>Leucovorin) |  |  |  |
|------------------------------------|--------------------------------------------------------------------|--|--|--|
| Subject group type                 | Reporting group                                                    |  |  |  |
| Number of subjects analysed        | 779                                                                |  |  |  |
| Units: subjects                    |                                                                    |  |  |  |
| Hyponatremia: All Grades (n= 736)  | 181                                                                |  |  |  |
| Hyponatremia: Grades 3-4 (n= 736)  | 32                                                                 |  |  |  |
| Hypernatremia: All Grades (n= 736) | 75                                                                 |  |  |  |

|                                   |     |  |  |  |
|-----------------------------------|-----|--|--|--|
| Hypernatremia: Grades 3-4 (n=736) | 1   |  |  |  |
| Hypocalcemia: All Grades (682)    | 213 |  |  |  |
| Hypocalcemia: Grades 3-4 (682)    | 5   |  |  |  |
| Hypercalcemia: All Grades (682)   | 52  |  |  |  |
| Hypercalcemia: Grades 3-4 (682)   | 2   |  |  |  |
| Hypokalemia: All Grades (734)     | 121 |  |  |  |
| Hypokalemia: Grades 3-4 (734)     | 16  |  |  |  |
| Hyperkalemia: All Grades (734)    | 166 |  |  |  |
| Hyperkalemia: Grades 3-4 (734)    | 10  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Abnormal Renal and Liver Function Parameters

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Abnormal Renal and Liver Function Parameters <sup>[5]</sup> |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Renal and liver function parameters included: creatinine, hyperbilirubinemia, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4) as per NCI CTCAE version 4.03, where Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                                           |                                                       |  |  |  |
|-------------------------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>                   | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type                        | Reporting group                                       |  |  |  |
| Number of subjects analysed               | 779                                                   |  |  |  |
| Units: subjects                           |                                                       |  |  |  |
| Creatinine: All Grades (n= 737)           | 161                                                   |  |  |  |
| Creatinine: Grades 3-4 (n= 737)           | 2                                                     |  |  |  |
| Hyperbilirubinemia: All Grades (n= 734)   | 130                                                   |  |  |  |
| Hyperbilirubinemia: Grades 3-4 (n= 734)   | 9                                                     |  |  |  |
| AST: All Grades (n= 727)                  | 342                                                   |  |  |  |
| AST: Grades 3-4 (n= 727)                  | 12                                                    |  |  |  |
| ALT: All Grades (n= 736)                  | 270                                                   |  |  |  |
| ALT: Grades 3-4 (n= 736)                  | 10                                                    |  |  |  |
| Alkaline phosphatase: All Grades (n= 733) | 465                                                   |  |  |  |
| Alkaline phosphatase: Grades 3-4 (n= 733) | 23                                                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Creatinine Clearance of Aflibercept Plus FOLFIRI

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Creatinine Clearance of Aflibercept Plus FOLFIRI <sup>[6]</sup> |
|-----------------|-----------------------------------------------------------------|

End point description:

Creatinine clearance is a measure of kidney function. Creatinine clearance rate is the volume of blood plasma that is cleared of creatinine by the kidneys per unit time. Creatinine clearance can be measured directly or estimated using established formulas. For this study, the creatinine clearance was calculated using the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD). Safety population. Here, subjects analysed = subjects evaluable for this end point.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

| End point values                     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
|--------------------------------------|-------------------------------------------------------|--|--|--|
| Subject group type                   | Reporting group                                       |  |  |  |
| Number of subjects analysed          | 312                                                   |  |  |  |
| Units: mL/min                        |                                                       |  |  |  |
| arithmetic mean (standard deviation) | 71.4 (± 29.3)                                         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Other Abnormal Biochemistry Parameters

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Number of Subjects With Other Abnormal Biochemistry Parameters <sup>[7]</sup> |
|-----------------|-------------------------------------------------------------------------------|

End point description:

Other abnormal biochemistry parameters included: hypoglycemia, hyperglycemia and hypoalbuminemia. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4) as per NCI CTCAE Version 4.03, where Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last)

comes last) (maximum exposure: 214 weeks)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                                      |                                                       |  |  |  |
|--------------------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>              | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type                   | Reporting group                                       |  |  |  |
| Number of subjects analysed          | 779                                                   |  |  |  |
| Units: subjects                      |                                                       |  |  |  |
| Hypoglycemia: All Grades (n= 725)    | 90                                                    |  |  |  |
| Hypoglycemia: Grades 3-4 (n= 725)    | 6                                                     |  |  |  |
| Hyperglycemia: All Grades (n= 725)   | 403                                                   |  |  |  |
| Hyperglycemia: Grades 3-4 (n= 725)   | 30                                                    |  |  |  |
| Hypoalbuminemia: All Grades (n= 689) | 241                                                   |  |  |  |
| Hypoalbuminemia: Grades 3-4 (n= 689) | 6                                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Abnormal Non-Gradable Biochemistry Parameters

|                 |                                                                                      |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Abnormal Non-Gradable Biochemistry Parameters <sup>[8]</sup> |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

Non-gradeable biochemistry parameters included; chloride, urea, total protein, blood urea nitrogen (BUN) and lactate dehydrogenase (LDH). Number of subjects with <lower limit of normal ranges (LLN) and >upper limit of normal ranges (ULN) for each of these parameters were reported. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                             |                                                       |  |  |  |
|-----------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type          | Reporting group                                       |  |  |  |
| Number of subjects analysed | 779                                                   |  |  |  |
| Units: subjects             |                                                       |  |  |  |
| Chloride<LLN (n= 711)       | 135                                                   |  |  |  |
| Chloride>ULN (n= 711)       | 217                                                   |  |  |  |
| BUN<LLN (n= 258)            | 41                                                    |  |  |  |
| BUN>ULN (n= 258)            | 83                                                    |  |  |  |

|                             |     |  |  |  |
|-----------------------------|-----|--|--|--|
| UREA<LLN (n= 591)           | 60  |  |  |  |
| UREA>ULN (n= 591)           | 250 |  |  |  |
| LDH<LLN (n= 723)            | 79  |  |  |  |
| LDH>ULN (n= 723)            | 423 |  |  |  |
| Total proteins<LLN (n= 711) | 162 |  |  |  |
| Total proteins>ULN (n= 711) | 77  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Proteinuria Events

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Number of Subjects With Proteinuria Events <sup>[9]</sup> |
|-----------------|-----------------------------------------------------------|

End point description:

Proteinuria is defined as the ratio of protein to creatinine. Number of subjects with proteinuria were analyzed by grades (Grades 1, 2, 3, 4) as per NCI CTCAE Version 4.03 where Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. Safety population.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                             |                                                       |  |  |  |
|-----------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type          | Reporting group                                       |  |  |  |
| Number of subjects analysed | 779                                                   |  |  |  |
| Units: subjects             |                                                       |  |  |  |
| Grade 1                     | 286                                                   |  |  |  |
| Grade 2                     | 123                                                   |  |  |  |
| Grade 3                     | 54                                                    |  |  |  |
| Grade 4                     | 5                                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Proteinuria Grade $\geq 2$

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Number of Subjects With Proteinuria Grade $\geq 2$ <sup>[10]</sup> |
|-----------------|--------------------------------------------------------------------|

End point description:

Proteinuria is defined as the ratio of protein to creatinine. Number of subjects with proteinuria grade  $\geq 2$  (graded as per NCI CTCAE Version 4.03), where Grade  $\geq 2$  represents moderate to life-threatening/disabling event. Safety population.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                             |                                                       |  |  |  |
|-----------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type          | Reporting group                                       |  |  |  |
| Number of subjects analysed | 779                                                   |  |  |  |
| Units: subjects             | 182                                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Urinary Protein-Creatinine Ratio (UPCR)

|                 |                                                                                 |
|-----------------|---------------------------------------------------------------------------------|
| End point title | Number of Subjects With Urinary Protein-Creatinine Ratio (UPCR) <sup>[11]</sup> |
|-----------------|---------------------------------------------------------------------------------|

End point description:

Urinary protein creatinine ratio (UPCR) corresponds to the ratio of the urinary protein and urinary creatinine concentration (expressed in mg/dL). This ratio provides an accurate quantification of 24-hours urinary protein excretion. There is a high correlation between morning UPCR and 24-hour proteinuria in subjects with normal or reduced renal functions. Normal ratio is  $< \text{ or } = 1$ . Safety population. Here 'n' signifies number of subjects with available data for specified categories.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                                    |                                                       |  |  |  |
|------------------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>            | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type                 | Reporting group                                       |  |  |  |
| Number of subjects analysed        | 779                                                   |  |  |  |
| Units: subjects                    |                                                       |  |  |  |
| UPCR $\leq 1$ (n= 367)             | 265                                                   |  |  |  |
| UPCR $\geq 1$ to $\leq 2$ (n= 367) | 51                                                    |  |  |  |
| UPCR $\geq 2$ to $\leq 3$ (n= 367) | 24                                                    |  |  |  |
| UPCR $> 3$ (n= 367)                | 27                                                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Proteinuria (Grade $\geq$ 2) Concomitant With Hematuria and /or Hypertension

|                 |                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Proteinuria (Grade $\geq$ 2) Concomitant With Hematuria and /or Hypertension <sup>[12]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------|

End point description:

Proteinuria is defined as the presence of excess proteins in the urine (assessed either by spot sample, dipstick/ urine protein or 24 hour urine collection). Hematuria is defined as the presence of blood in urine (positive dipstick for RBC or reported AE). Number of subjects with proteinuria grade  $\geq$ 2 (graded as per NCI CTCAE Version 4.03), where Grade $\geq$ 2 represents moderate to life-threatening/disabling event. Hypertension (high blood pressure) is defined as having a blood pressure reading of more than 140/90 mmHg over a number of weeks. Safety population.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                                             |                                                       |  |  |  |
|---------------------------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>                     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type                          | Reporting group                                       |  |  |  |
| Number of subjects analysed                 | 779                                                   |  |  |  |
| Units: subjects                             |                                                       |  |  |  |
| Proteinuria with hematuria                  | 72                                                    |  |  |  |
| Proteinuria with hypertension               | 4                                                     |  |  |  |
| Proteinuria with hematuria and hypertension | 3                                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Cycle Delay and/or Dose Modification

|                 |                                                 |
|-----------------|-------------------------------------------------|
| End point title | Number of Subjects With Cycle Delay and/or Dose |
|-----------------|-------------------------------------------------|

End point description:

A theoretical cycle is a 2 week period i.e. 14 days. A cycle is delayed if duration of previous cycle is greater than 14+2 days ; dose modification includes dose reduction and dose omission. Safety population defined as the subjects who signed the informed consent form and received at least one dose of study treatment.

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

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)



Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

|                                               |                                                                    |  |  |  |
|-----------------------------------------------|--------------------------------------------------------------------|--|--|--|
| <b>End point values</b>                       | Aflibercept +<br>FOLFIRI<br>(Irinotecan, 5-<br>FU &<br>Leucovorin) |  |  |  |
| Subject group type                            | Reporting group                                                    |  |  |  |
| Number of subjects analysed                   | 779                                                                |  |  |  |
| Units: Subjects                               |                                                                    |  |  |  |
| No delay and no dose modification             | 119                                                                |  |  |  |
| Any delay and/or dose modification            | 660                                                                |  |  |  |
| Delay only                                    | 163                                                                |  |  |  |
| Delay and Aflibercept modified                | 39                                                                 |  |  |  |
| Delay and FOLFIRI modified                    | 308                                                                |  |  |  |
| Delay and Aflibercept and Folfiri<br>modified | 97                                                                 |  |  |  |
| Only Aflibercept modified                     | 5                                                                  |  |  |  |
| Only FOLFIRI modified                         | 43                                                                 |  |  |  |
| Both Aflibercept and FOLFIRI modified         | 5                                                                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline in Health Related Quality of Life (HRQL) European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30 Score): Global Health Status

|                 |                                                                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean Change From Baseline in Health Related Quality of Life (HRQL) European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30 Score): Global Health Status |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

EORTC-QLQ-C30: cancer-specific instrument with 30 questions(Q). First 28 Q used 4-point scale(S)(1=not at all,2=a little,3=quite a bit,4=very much)for evaluating 5 functional S(physical,role,emotional,cognitive,social),3 symptom S (fatigue,nausea/vomiting,pain) & other single items. For each item,high score=high level symptomatology.Last 2Q=subject's assessment of overall health & quality of life (qol) on 7-point S(1=very poor to 7=excellent).EORTC QLQ-C30 observed values & change from baseline(B) for global health status (scoring of Q 29 & 30) & 5 functional S,3 symptom S & other single items (scoring of Q1 to 28). Answers converted into grading S, with values between 0 & 100. High score=favourable outcome with best qol for subject. EORTC QLQ-C30 analysis population:subjects who signed informed consent form; had evaluable QLQ-C30 questionnaire at B & >=1 evaluable assessment post B & received at least part of 1 dose of study treatment.'n'= subjects analysed at specified time-points.

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

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at the end of treatment (EOT) (within 30 days of last treatment) (maximum exposure: 214 weeks)

|                                      |                                                                    |  |  |  |
|--------------------------------------|--------------------------------------------------------------------|--|--|--|
| <b>End point values</b>              | Aflibercept +<br>FOLFIRI<br>(Irinotecan, 5-<br>FU &<br>Leucovorin) |  |  |  |
| Subject group type                   | Reporting group                                                    |  |  |  |
| Number of subjects analysed          | 636                                                                |  |  |  |
| Units: units on a scale              |                                                                    |  |  |  |
| arithmetic mean (standard deviation) |                                                                    |  |  |  |
| Baseline (n= 630)                    | 68.61 (±<br>20.48)                                                 |  |  |  |
| Change at Cycle 3 (n= 549)           | -3.34 (±<br>18.83)                                                 |  |  |  |
| Change at Cycle 5 (n= 429)           | -4.70 (±<br>18.89)                                                 |  |  |  |
| Change at Cycle 7 (n= 344)           | -3.63 (±<br>22.02)                                                 |  |  |  |
| Change at Cycle 9 (n= 273)           | -3.97 (±<br>21.31)                                                 |  |  |  |
| Change at Cycle 11 (n= 232)          | -5.85 (±<br>22.26)                                                 |  |  |  |
| Change at Cycle 13 (n= 151)          | -2.26 (±<br>21.69)                                                 |  |  |  |
| Change at Cycle 15 (n= 123)          | -3.05 (±<br>22.46)                                                 |  |  |  |
| Change at Cycle 17 (n= 85)           | -1.18 (±<br>22.50)                                                 |  |  |  |
| Change at Cycle 19 (n= 60)           | -2.36 (±<br>22.92)                                                 |  |  |  |
| Change at Cycle 21 (n= 45)           | -5.56 (±<br>23.77)                                                 |  |  |  |
| Change at Cycle 23 (n= 34)           | -6.86 (±<br>19.94)                                                 |  |  |  |
| Change at Cycle 25 (n= 29)           | -8.05 (±<br>16.89)                                                 |  |  |  |
| Change at Cycle 27 (n= 23)           | -10.14 (±<br>17.58)                                                |  |  |  |
| Change at Cycle 29 (n= 20)           | -8.33 (±<br>14.05)                                                 |  |  |  |
| Change at Cycle 31 (n= 15)           | -9.44 (±<br>16.92)                                                 |  |  |  |
| Change at Cycle 33 (n= 11)           | -11.36 (±<br>21.82)                                                |  |  |  |
| Change at Cycle 35 (n =10)           | -5.83 (±<br>20.81)                                                 |  |  |  |
| Change at EOT (n= 340)               | -8.82 (±<br>23.95)                                                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline in HRQL EORTC QLQ-C30 Score: Functional Scales

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Mean Change From Baseline in HRQL EORTC QLQ-C30 Score: Functional Scales |
|-----------------|--------------------------------------------------------------------------|

End point description:

EORTC-QLQ-C30: cancer-specific instrument with 30 questions (Q) for evaluation of new chemotherapy & provides an assessment of subject reported outcome dimensions. First 28 Q used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much) for evaluating 5 functional scales (physical, role, emotional, cognitive, social), 3 symptom scales (fatigue, nausea/vomiting, pain) & other single items. For each item, high score=high level of symptomatology/problem. Last 2 Q=subject's assessment of overall health & quality of life, coded on 7-point scale (1=very poor to 7=excellent). EORTC QLQ-C30 observed values & change from baseline for global health status (scoring of Q 29 & 30) & 5 functional scales, 3 symptom scales & other single items (scoring of Q 1 to 28). Answers were converted into grading scale, with values between 0 & 100. High score=favourable outcome with a best quality of life for subject. EORTC QLQ-C30 analysis population. 'n' signifies =subjects analysed at

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

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

| End point values                       | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
|----------------------------------------|-------------------------------------------------------|--|--|--|
| Subject group type                     | Reporting group                                       |  |  |  |
| Number of subjects analysed            | 636                                                   |  |  |  |
| Units: units on a scale                |                                                       |  |  |  |
| arithmetic mean (standard deviation)   |                                                       |  |  |  |
| Physical - Baseline (n= 634)           | 81.79 (± 19.41)                                       |  |  |  |
| Physical - Change at Cycle 3 (n= 551)  | -3.73 (± 15.15)                                       |  |  |  |
| Physical - Change at Cycle 5 (n= 439)  | -3.95 (± 15.22)                                       |  |  |  |
| Physical - Change at Cycle 7 (n= 342)  | -4.62 (± 16.23)                                       |  |  |  |
| Physical - Change at Cycle 9 (n= 275)  | -4.36 (± 15.79)                                       |  |  |  |
| Physical - Change at Cycle 11 (n= 235) | -6.99 (± 17.89)                                       |  |  |  |
| Physical - Change at Cycle 13 (n= 154) | -4.99 (± 16.17)                                       |  |  |  |
| Physical - Change at Cycle 15 (n= 122) | -3.54 (± 15.99)                                       |  |  |  |
| Physical - Change at Cycle 17 (n= 87)  | -5.10 (± 16.20)                                       |  |  |  |
| Physical - Change at Cycle 19 (n= 61)  | -5.68 (± 16.23)                                       |  |  |  |
| Physical - Change at Cycle 21 (n= 46)  | -5.70 (± 13.01)                                       |  |  |  |
| Physical - Change at Cycle 23 (n= 36)  | -7.87 (± 14.38)                                       |  |  |  |
| Physical - Change at Cycle 25 (n= 29)  | -5.75 (± 12.18)                                       |  |  |  |
| Physical - Change at Cycle 27 (n= 23)  | -6.59 (± 11.64)                                       |  |  |  |
| Physical - Change at Cycle 29 (n= 20)  | -7.67 (± 11.09)                                       |  |  |  |
| Physical - Change at Cycle 31 (n= 15)  | -9.33 (± 14.65)                                       |  |  |  |
| Physical - Change at Cycle 33 (n= 11)  | -5.45 (± 9.81)                                        |  |  |  |

|                                         |                  |  |  |  |
|-----------------------------------------|------------------|--|--|--|
| Physical - Change at Cycle 35 (n= 10)   | -10.00 (± 13.05) |  |  |  |
| Physical - Change at EOT (n= 341)       | -11.16 (± 21.65) |  |  |  |
| Role - Baseline (n= 633)                | 79.91 (± 26.25)  |  |  |  |
| Role - Change at Cycle 3 (n= 551)       | -6.26 (± 25.22)  |  |  |  |
| Role - Change at Cycle 5 (n= 442)       | -5.66 (± 23.26)  |  |  |  |
| Role - Change at Cycle 7 (n= 342)       | -6.68 (± 24.29)  |  |  |  |
| Role - Change at Cycle 9 (n= 275)       | -6.55 (± 23.95)  |  |  |  |
| Role - Change at Cycle 11 (n= 234)      | -8.76 (± 26.35)  |  |  |  |
| Role - Change at Cycle 13 (n= 154)      | -7.36 (± 23.41)  |  |  |  |
| Role - Change at Cycle 15 (n= 123)      | -7.18 (± 21.98)  |  |  |  |
| Role - Change at Cycle 17 (n= 87)       | -9.58 (± 22.54)  |  |  |  |
| Role - Change at Cycle 19 (n= 61)       | -9.84 (± 22.44)  |  |  |  |
| Role - Change at Cycle 21 (n= 46)       | -9.78 (± 18.11)  |  |  |  |
| Role - Change at Cycle 23 (n= 36)       | -10.65 (± 18.32) |  |  |  |
| Role - Change at Cycle 25 (n= 29)       | -10.92 (± 17.97) |  |  |  |
| Role - Change at Cycle 27 (n= 23)       | -10.14 (± 17.22) |  |  |  |
| Role - Change at Cycle 29 (n= 20)       | -10.83 (± 17.33) |  |  |  |
| Role - Change at Cycle 31 (n= 15)       | -14.44 (± 18.76) |  |  |  |
| Role - Change at Cycle 33 (n= 11)       | -15.15 (± 15.73) |  |  |  |
| Role - Change at Cycle 35 (n= 10)       | -15.00 (± 16.57) |  |  |  |
| Role - Change at EOT (n= 340)           | -12.11 (± 28.22) |  |  |  |
| Emotional - Baseline (n= 634)           | 78.96 (± 20.60)  |  |  |  |
| Emotional - Change at Cycle 3 (n= 553)  | 1.14 (± 19.95)   |  |  |  |
| Emotional - Change at Cycle 5 (n= 436)  | 0.74 (± 19.32)   |  |  |  |
| Emotional - Change at Cycle 7 (n= 344)  | 1.58 (± 20.91)   |  |  |  |
| Emotional - Change at Cycle 9 (n= 275)  | 1.69 (± 21.38)   |  |  |  |
| Emotional - Change at Cycle 11 (n= 235) | 0.08 (± 20.40)   |  |  |  |
| Emotional - Change at Cycle 13 (n= 152) | 0.93 (± 20.08)   |  |  |  |
| Emotional - Change at Cycle 15 (n= 124) | 2.51 (± 20.23)   |  |  |  |
| Emotional - Change at Cycle 17 (n= 87)  | 2.91 (± 18.23)   |  |  |  |
| Emotional - Change at Cycle 19 (n= 60)  | 1.39 (± 17.60)   |  |  |  |
| Emotional - Change at Cycle 21 (n= 44)  | 0.06 (± 17.86)   |  |  |  |
| Emotional - Change at Cycle 23 (n= 35)  | 1.75 (± 19.29)   |  |  |  |
| Emotional - Change at Cycle 25 (n= 29)  | 4.98 (± 15.86)   |  |  |  |
| Emotional - Change at Cycle 27 (n= 23)  | 1.57 (± 17.64)   |  |  |  |

|                                         |                  |  |  |  |
|-----------------------------------------|------------------|--|--|--|
| Emotional - Change at Cycle 29 (n= 20)  | 2.64 (± 17.88)   |  |  |  |
| Emotional - Change at Cycle 31 (n= 15)  | 1.30 (± 17.78)   |  |  |  |
| Emotional - Change at Cycle 33 (n= 11)  | 0.25 (± 3.82)    |  |  |  |
| Emotional - Change at Cycle 35 (n= 10)  | -0.00 (± 5.56)   |  |  |  |
| Emotional - Change at EOT (n= 345)      | -2.87 (± 22.52)  |  |  |  |
| Cognitive - Baseline (n= 635)           | 86.90 (± 19.26)  |  |  |  |
| Cognitive - Change at Cycle 3 (n= 555)  | -1.77 (± 16.92)  |  |  |  |
| Cognitive - Change at Cycle 5 (n= 437)  | -1.87 (± 16.58)  |  |  |  |
| Cognitive - Change at Cycle 7 (n= 343)  | -1.99 (± 19.71)  |  |  |  |
| Cognitive - Change at Cycle 9 (n= 275)  | -2.18 (± 20.17)  |  |  |  |
| Cognitive - Change at Cycle 11 (n= 234) | -4.27 (± 20.29)  |  |  |  |
| Cognitive - Change at Cycle 13 (n= 153) | -2.83 (± 17.40)  |  |  |  |
| Cognitive - Change at Cycle 15 (n= 124) | -2.28 (± 19.40)  |  |  |  |
| Cognitive - Change at Cycle 17 (n= 87)  | -3.45 (± 19.38)  |  |  |  |
| Cognitive - Change at Cycle 19 (n= 60)  | -5.00 (± 22.19)  |  |  |  |
| Cognitive - Change at Cycle 21 (n= 45)  | -5.56 (± 16.28)  |  |  |  |
| Cognitive - Change at Cycle 23 (n= 35)  | -5.71 (± 14.54)  |  |  |  |
| Cognitive - Change at Cycle 25 (n= 29)  | -6.90 (± 21.14)  |  |  |  |
| Cognitive - Change at Cycle 27 (n= 23)  | -5.80 (± 16.37)  |  |  |  |
| Cognitive - Change at Cycle 29 (n= 20)  | -6.67 (± 18.26)  |  |  |  |
| Cognitive - Change at Cycle 31 (n= 15)  | -5.56 (± 15.00)  |  |  |  |
| Cognitive - Change at Cycle 33 (n= 11)  | -10.61 (± 17.12) |  |  |  |
| Cognitive - Change at Cycle 35 (n= 10)  | -11.67 (± 13.72) |  |  |  |
| Cognitive- Change at EOT (n= 345)       | -4.98 (± 22.67)  |  |  |  |
| Social - Baseline (n= 634)              | 80.57 (± 24.68)  |  |  |  |
| Social - Change at Cycle 3 (n= 554)     | -2.05 (± 22.83)  |  |  |  |
| Social - Change at Cycle 5 (n= 437)     | -2.86 (± 21.60)  |  |  |  |
| Social - Change at Cycle 7 (n= 345)     | -4.78 (± 23.65)  |  |  |  |
| Social - Change at Cycle 9 (n= 274)     | -4.56 (± 23.84)  |  |  |  |
| Social - Change at Cycle 11 (n= 235)    | -7.09 (± 24.83)  |  |  |  |
| Social - Change at Cycle 13 (n= 153)    | -5.56 (± 24.03)  |  |  |  |
| Social - Change at Cycle 15 (n= 124)    | -6.18 (± 23.23)  |  |  |  |

|                                     |                 |  |  |  |
|-------------------------------------|-----------------|--|--|--|
| Social - Change at Cycle 17 (n= 87) | -5.56 (± 22.69) |  |  |  |
| Social - Change at Cycle 19 (n= 60) | -5.28 (± 22.02) |  |  |  |
| Social - Change at Cycle 21 (n= 45) | -5.56 (± 21.61) |  |  |  |
| Social - Change at Cycle 23 (n= 35) | -7.62 (± 17.78) |  |  |  |
| Social - Change at Cycle 25 (n= 29) | -4.60 (± 18.31) |  |  |  |
| Social - Change at Cycle 27 (n= 23) | -2.17 (± 17.63) |  |  |  |
| Social - Change at Cycle 29 (n= 20) | -5.00 (± 18.81) |  |  |  |
| Social - Change at Cycle 31 (n= 15) | -7.78 (± 25.09) |  |  |  |
| Social - Change at Cycle 33 (n= 11) | -1.52 (± 17.41) |  |  |  |
| Social - Change at Cycle 35 (n= 10) | -1.67 (± 14.59) |  |  |  |
| Social - Change at EOT (n= 344)     | -9.01 (± 26.23) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in HRQL EORTC QLQ-C30 Score: Symptom Scales

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Change From Baseline in HRQL EORTC QLQ-C30 Score: Symptom Scales |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                  |
| EORTC-QLQ-C30:cancer-specific instrument with 30 questions (Q) for evaluation of new chemotherapy & provides an assessment of subjects reported outcome dimensions. First 28 Q used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much) for evaluating 5 functional scales (physical,role,emotional,cognitive,social), 3 symptom scales (fatigue,nausea/vomiting,pain) & other single items. For each item,high score=high level of symptomatology/problem. Last 2 Q=subject's assessment of overall health & quality of life, coded on 7-point scale (1=very poor to 7=excellent). EORTC QLQ-C30 observed values & change from baseline for global health status (scoring of Q 29 & 30) & 5 functional scales, 3 symptom scales & other single items (scoring of Q 1 to 28). Answers were converted into grading scale, with values between 0 and 100. A high score=favorable outcome with a best quality of life for subject. EORTC QLQ-C30 analysis population. Here, `n`=subjects analysed at |                                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                                                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                  |
| Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                  |

|                             |                                                       |  |  |  |
|-----------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type          | Reporting group                                       |  |  |  |
| Number of subjects analysed | 636                                                   |  |  |  |
| Units: units on a scale     |                                                       |  |  |  |

| arithmetic mean (standard deviation)              |                 |  |  |  |
|---------------------------------------------------|-----------------|--|--|--|
| Fatigue - Baseline (n= 633)                       | 29.16 (± 23.48) |  |  |  |
| Fatigue - Change at Cycle 3 (n =551)              | 7.35 (± 21.62)  |  |  |  |
| Fatigue - Change at Cycle 5 (n= 443)              | 8.40 (± 21.88)  |  |  |  |
| Fatigue - Change at Cycle 7 (n= 344)              | 9.54 (± 22.60)  |  |  |  |
| Fatigue - Change at Cycle 9 (n= 276)              | 7.89 (± 21.80)  |  |  |  |
| Fatigue - Change at Cycle 11 (n= 235)             | 11.30 (± 23.73) |  |  |  |
| Fatigue - Change at Cycle 13 (n= 154)             | 8.33 (± 21.72)  |  |  |  |
| Fatigue - Change at Cycle 15 (n= 123)             | 7.41 (± 22.38)  |  |  |  |
| Fatigue - Change at Cycle 17 (n= 87)              | 6.70 (± 21.25)  |  |  |  |
| Fatigue - Change at Cycle 19 (n= 61)              | 8.93 (± 19.83)  |  |  |  |
| Fatigue - Change at Cycle 21 (n= 46)              | 10.39 (± 17.90) |  |  |  |
| Fatigue - Change at Cycle 23 (n= 36)              | 10.80 (± 18.49) |  |  |  |
| Fatigue - Change at Cycle 25 (n= 29)              | 7.66 (± 19.94)  |  |  |  |
| Fatigue - Change at Cycle 27 (n= 23)              | 9.66 (± 18.74)  |  |  |  |
| Fatigue - Change at Cycle 29 (n= 20)              | 11.67 (± 18.55) |  |  |  |
| Fatigue - Change at Cycle 31 (n= 15)              | 14.07 (± 21.61) |  |  |  |
| Fatigue - Change at Cycle 33 (n= 11)              | 15.15 (± 21.81) |  |  |  |
| Fatigue - Change at Cycle 35 (n= 10)              | 14.44 (± 18.92) |  |  |  |
| Fatigue - Change at EOT (n= 343)                  | 12.31 (± 25.56) |  |  |  |
| Nausea and Vomiting - Baseline (n= 635)           | 5.88 (± 13.99)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 3 (n= 554)  | 6.68 (± 19.81)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 5 (n= 442)  | 6.98 (± 19.79)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 7 (n= 343)  | 6.61 (± 18.07)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 9 (n= 277)  | 6.20 (± 19.68)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 11 (n= 236) | 8.97 (± 19.83)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 13 (n= 154) | 6.82 (± 14.71)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 15 (n= 124) | 6.85 (± 16.33)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 17 (n= 87)  | 3.45 (± 15.49)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 19 (n= 61)  | 6.56 (± 14.04)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 21 (n= 46)  | 3.99 (± 14.14)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 23 (n= 36)  | 7.87 (± 10.90)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 25 (n= 29)  | 4.02 (± 8.52)   |  |  |  |
| Nausea and Vomiting - Change at Cycle 27 (n= 23)  | 7.25 (± 11.04)  |  |  |  |
| Nausea and Vomiting - Change at Cycle 29 (n= 20)  | 1.67 (± 5.13)   |  |  |  |

|                                                  |                 |  |  |  |
|--------------------------------------------------|-----------------|--|--|--|
| Nausea and Vomiting - Change at Cycle 31 (n= 15) | 13.33 (± 28.31) |  |  |  |
| Nausea and Vomiting - Change at Cycle 33 (n= 11) | 3.03 (± 6.74)   |  |  |  |
| Nausea and Vomiting - Change at Cycle 35 (n= 10) | 3.33 (± 7.03)   |  |  |  |
| Nausea and Vomiting - Change at EOT (n= 344)     | 6.64 (± 21.11)  |  |  |  |
| Pain - Baseline (n= 636)                         | 20.47 (± 25.08) |  |  |  |
| Pain - Change at Cycle 3 (n= 554)                | 2.68 (± 25.02)  |  |  |  |
| Pain - Change at Cycle 5 (n= 444)                | 2.52 (± 23.48)  |  |  |  |
| Pain - Change at Cycle 7 (n= 345)                | 3.00 (± 24.98)  |  |  |  |
| Pain - Change at Cycle 9 (n= 276)                | 2.72 (± 24.45)  |  |  |  |
| Pain - Change at Cycle 11 (n= 236)               | 6.64 (± 23.68)  |  |  |  |
| Pain - Change at Cycle 13 (n= 155)               | 5.16 (± 19.79)  |  |  |  |
| Pain - Change at Cycle 15 (n= 124)               | 7.26 (± 21.91)  |  |  |  |
| Pain - Change at Cycle 17 (n= 87)                | 9.39 (± 22.97)  |  |  |  |
| Pain - Change at Cycle 19 (n= 61)                | 8.74 (± 22.28)  |  |  |  |
| Pain - Change at Cycle 21 (n= 46)                | 7.25 (± 18.14)  |  |  |  |
| Pain - Change at Cycle 23 (n= 36)                | 8.33 (± 19.31)  |  |  |  |
| Pain - Change at Cycle 25 (n= 29)                | 5.75 (± 21.02)  |  |  |  |
| Pain - Change at Cycle 27 (n= 23)                | 5.07 (± 17.72)  |  |  |  |
| Pain - Change at Cycle 29 (n= 20)                | 4.17 (± 16.11)  |  |  |  |
| Pain - Change at Cycle 31 (n= 15)                | 10.00 (± 23.40) |  |  |  |
| Pain - Change at Cycle 33 (n= 11)                | 7.58 (± 22.81)  |  |  |  |
| Pain - Change at Cycle 35 (n= 10)                | 6.67 (± 21.08)  |  |  |  |
| Pain - Change at EOT (n= 347)                    | 10.85 (± 28.99) |  |  |  |
| Dyspnoea - Baseline (n= 627)                     | 13.45 (± 22.01) |  |  |  |
| Dyspnoea - Change at Cycle 3 (n= 542)            | 3.63 (± 22.96)  |  |  |  |
| Dyspnoea - Change at Cycle 5 (n= 435)            | 5.75 (± 24.06)  |  |  |  |
| Dyspnoea - Change at Cycle 7 (n= 339)            | 6.98 (± 24.47)  |  |  |  |
| Dyspnoea - Change at Cycle 9 (n= 271)            | 6.89 (± 24.38)  |  |  |  |
| Dyspnoea - Change at Cycle 11 (n= 232)           | 8.19 (± 26.59)  |  |  |  |
| Dyspnoea - Change at Cycle 13 (n= 152)           | 6.36 (± 25.37)  |  |  |  |
| Dyspnoea - Change at Cycle 15 (n= 121)           | 3.58 (± 24.65)  |  |  |  |
| Dyspnoea - Change at Cycle 17 (n= 84)            | 5.16 (± 24.54)  |  |  |  |
| Dyspnoea - Change at Cycle 19 (n= 59)            | 6.78 (± 26.82)  |  |  |  |
| Dyspnoea - Change at Cycle 21 (n= 44)            | 3.79 (± 22.98)  |  |  |  |
| Dyspnoea - Change at Cycle 23 (n= 33)            | 4.04 (± 20.00)  |  |  |  |
| Dyspnoea - Change at Cycle 25 (n= 27)            | 1.23 (± 21.64)  |  |  |  |
| Dyspnoea - Change at Cycle 27 (n= 22)            | 3.03 (± 22.79)  |  |  |  |
| Dyspnoea - Change at Cycle 29 (n= 19)            | -1.75 (± 23.50) |  |  |  |
| Dyspnoea - Change at Cycle 31 (n= 14)            | 16.67 (± 28.50) |  |  |  |
| Dyspnoea - Change at Cycle 33 (n= 10)            | 16.67 (± 17.57) |  |  |  |
| Dyspnoea - Change at Cycle 35 (n= 10)            | 16.67 (± 23.57) |  |  |  |
| Dyspnoea - Change at EOT (n= 337)                | 6.53 (± 25.79)  |  |  |  |



|                                             |                 |  |  |  |
|---------------------------------------------|-----------------|--|--|--|
| Insomnia - Baseline (n= 628)                | 24.15 (± 28.09) |  |  |  |
| Insomnia - Change at Cycle 3 (n= 544)       | 0.37 (± 27.36)  |  |  |  |
| Insomnia - Change at Cycle 5 (n= 438)       | -0.08 (± 28.48) |  |  |  |
| Insomnia - Change at Cycle 7 (n= 338)       | -2.37 (± 29.63) |  |  |  |
| Insomnia - Change at Cycle 9 (n= 274)       | -0.24 (± 29.37) |  |  |  |
| Insomnia - Change at Cycle 11 (n= 234)      | 2.56 (± 28.86)  |  |  |  |
| Insomnia - Change at Cycle 13 (n= 153)      | 0.65 (± 26.89)  |  |  |  |
| Insomnia - Change at Cycle 15 (n= 122)      | -2.19 (± 27.01) |  |  |  |
| Insomnia - Change at Cycle 17 (n= 87)       | -1.92 (± 25.60) |  |  |  |
| Insomnia - Change at Cycle 19 (n= 61)       | 1.64 (± 23.12)  |  |  |  |
| Insomnia - Change at Cycle 21 (n= 45)       | 0.74 (± 25.11)  |  |  |  |
| Insomnia - Change at Cycle 23 (n= 36)       | -0.93 (± 33.32) |  |  |  |
| Insomnia - Change at Cycle 25 (n= 29)       | -0.00 (± 28.17) |  |  |  |
| Insomnia - Change at Cycle 27 (n= 22)       | -1.52 (± 24.07) |  |  |  |
| Insomnia - Change at Cycle 29 (n= 20)       | -3.33 (± 30.40) |  |  |  |
| Insomnia - Change at Cycle 31 (n= 15)       | -4.44 (± 41.53) |  |  |  |
| Insomnia - Change at Cycle 33 (n= 11)       | -6.06 (± 32.72) |  |  |  |
| Insomnia - Change at Cycle 35 (n= 10)       | -3.33 (± 33.15) |  |  |  |
| Insomnia - Change at EOT (n= 339)           | 5.31 (± 32.50)  |  |  |  |
| Appetite loss - Baseline (n= 631)           | 17.38 (± 26.01) |  |  |  |
| Appetite loss - Change at Cycle 3 (n= 546)  | 9.10 (± 28.64)  |  |  |  |
| Appetite loss - Change at Cycle 5 (n= 436)  | 9.02 (± 28.14)  |  |  |  |
| Appetite loss - Change at Cycle 7 (n= 342)  | 9.84 (± 27.80)  |  |  |  |
| Appetite loss - Change at Cycle 9 (n= 274)  | 9.98 (± 27.18)  |  |  |  |
| Appetite loss - Change at Cycle 11 (n= 234) | 14.53 (± 28.27) |  |  |  |
| Appetite loss - Change at Cycle 13 (n= 150) | 10.67 (± 27.12) |  |  |  |
| Appetite loss - Change at Cycle 15 (n= 121) | 10.74 (± 25.90) |  |  |  |
| Appetite loss - Change at Cycle 17 (n= 86)  | 8.91 (± 24.75)  |  |  |  |
| Appetite loss - Change at Cycle 19 (n= 61)  | 9.84 (± 24.60)  |  |  |  |
| Appetite loss - Change at Cycle 21 (n= 46)  | 13.04 (± 25.80) |  |  |  |
| Appetite loss - Change at Cycle 23 (n= 35)  | 12.38 (± 25.67) |  |  |  |
| Appetite loss - Change at Cycle 25 (n= 29)  | 11.49 (± 20.46) |  |  |  |

|                                            |                 |  |  |  |
|--------------------------------------------|-----------------|--|--|--|
| Appetite loss - Change at Cycle 27 (n= 23) | 15.94 (± 22.18) |  |  |  |
| Appetite loss - Change at Cycle 29 (n= 20) | 15.00 (± 20.16) |  |  |  |
| Appetite loss - Change at Cycle 31 (n= 15) | 15.56 (± 24.77) |  |  |  |
| Appetite loss - Change at Cycle 33 (n= 11) | 15.15 (± 22.92) |  |  |  |
| Appetite loss - Change at Cycle 35 (n= 10) | 16.67 (± 17.57) |  |  |  |
| Appetite loss - Change at EOT (n= 338)     | 12.03 (± 33.48) |  |  |  |
| Constipation - Baseline (n= 632)           | 12.71 (± 21.61) |  |  |  |
| Constipation - Change at Cycle 3 (n= 550)  | 2.42 (± 25.25)  |  |  |  |
| Constipation - Change at Cycle 5 (n= 433)  | 3.77 (± 26.52)  |  |  |  |
| Constipation - Change at Cycle 7 (n= 342)  | 2.63 (± 26.09)  |  |  |  |
| Constipation - Change at Cycle 9 (n= 274)  | 5.35 (± 26.68)  |  |  |  |
| Constipation - Change at Cycle 11 (n= 234) | 4.42 (± 26.47)  |  |  |  |
| Constipation - Change at Cycle 13 (n= 153) | 4.58 (± 25.95)  |  |  |  |
| Constipation - Change at Cycle 15 (n= 122) | 4.92 (± 26.30)  |  |  |  |
| Constipation - Change at Cycle 17 (n= 86)  | 5.43 (± 23.35)  |  |  |  |
| Constipation - Change at Cycle 19 (n= 60)  | 8.33 (± 21.81)  |  |  |  |
| Constipation - Change at Cycle 21 (n= 44)  | 6.06 (± 18.00)  |  |  |  |
| Constipation - Change at Cycle 23 (n= 36)  | 9.26 (± 21.98)  |  |  |  |
| Constipation - Change at Cycle 25 (n= 29)  | 5.75 (± 17.97)  |  |  |  |
| Constipation - Change at Cycle 27 (n= 23)  | 1.45 (± 12.22)  |  |  |  |
| Constipation - Change at Cycle 29 (n= 20)  | 6.67 (± 20.52)  |  |  |  |
| Constipation - Change at Cycle 31 (n= 15)  | 22.22 (± 32.53) |  |  |  |
| Constipation - Change at Cycle 33 (n= 11)  | 12.12 (± 16.82) |  |  |  |
| Constipation - Change at Cycle 35 (n= 10)  | 10.00 (± 16.10) |  |  |  |
| Constipation - Change at EOT (n= 344)      | 3.78 (± 27.33)  |  |  |  |
| Diarrhoea - Baseline (n= 633)              | 10.37 (± 19.47) |  |  |  |
| Diarrhoea - Change at Cycle 3 (n= 549)     | 11.72 (± 28.16) |  |  |  |
| Diarrhoea - Change at Cycle 5 (n= 433)     | 10.85 (± 28.29) |  |  |  |
| Diarrhoea - Change at Cycle 7 (n= 344)     | 14.63 (± 29.94) |  |  |  |
| Diarrhoea - Change at Cycle 9 (n= 274)     | 11.44 (± 26.44) |  |  |  |
| Diarrhoea - Change at Cycle 11 (n= 235)    | 15.46 (± 27.26) |  |  |  |

|                                                     |                 |  |  |  |
|-----------------------------------------------------|-----------------|--|--|--|
| Diarrhoea - Change at Cycle 13 (n= 151)             | 11.26 (± 24.00) |  |  |  |
| Diarrhoea - Change at Cycle 15 (n= 121)             | 11.02 (± 28.02) |  |  |  |
| Diarrhoea - Change at Cycle 17 (n= 87)              | 10.34 (± 21.75) |  |  |  |
| Diarrhoea - Change at Cycle 19 (n= 59)              | 15.25 (± 25.76) |  |  |  |
| Diarrhoea - Change at Cycle 21 (n= 45)              | 14.07 (± 24.09) |  |  |  |
| Diarrhoea - Change at Cycle 23 (n= 36)              | 18.52 (± 21.74) |  |  |  |
| Diarrhoea - Change at Cycle 25 (n= 29)              | 10.34 (± 22.01) |  |  |  |
| Diarrhoea - Change at Cycle 27 (n= 22)              | 13.64 (± 19.68) |  |  |  |
| Diarrhoea - Change at Cycle 29 (n= 20)              | 16.67 (± 25.36) |  |  |  |
| Diarrhoea - Change at Cycle 31 (n= 15)              | 20.00 (± 24.56) |  |  |  |
| Diarrhoea - Change at Cycle 33 (n= 11)              | 18.18 (± 22.92) |  |  |  |
| Diarrhoea - Change at Cycle 35 (n= 10)              | 30.00 (± 18.92) |  |  |  |
| Diarrhoea - Change at EOT (n= 342)                  | 7.31 (± 24.26)  |  |  |  |
| Financial difficulties - Baseline (n= 628)          | 20.12 (± 30.25) |  |  |  |
| Financial difficulties - Change at Cycle 3 (n= 547) | -1.83 (± 23.80) |  |  |  |
| Financial difficulties - Change at Cycle 5 (n=430)  | -1.32 (± 24.00) |  |  |  |
| Financial difficulties - Change at Cycle 7 (n=337)  | -0.99 (± 27.68) |  |  |  |
| Financial difficulties - Change at Cycle 9 (n=270)  | -0.49 (± 26.80) |  |  |  |
| Financial difficulties - Change at Cycle 11(n=232)  | 3.30 (± 25.64)  |  |  |  |
| Financial difficulties - Change at Cycle 13(n=150)  | 1.11 (± 27.96)  |  |  |  |
| Financial difficulties - Change at Cycle 15(n=122)  | -0.27 (± 27.94) |  |  |  |
| Financial difficulties - Change at Cycle 17 (n=87)  | 0.77 (± 27.36)  |  |  |  |
| Financial difficulties - Change at Cycle 19 (n=60)  | 1.67 (± 29.70)  |  |  |  |
| Financial difficulties - Change at Cycle 21 (n=45)  | 4.44 (± 25.23)  |  |  |  |
| Financial difficulties - Change at Cycle 23 (n=34)  | 2.94 (± 23.74)  |  |  |  |
| Financial difficulties - Change at Cycle 25 (n=29)  | -4.60 (± 19.36) |  |  |  |
| Financial difficulties - Change at Cycle 27 (n=23)  | -2.90 (± 24.44) |  |  |  |
| Financial difficulties - Change at Cycle 29 (n=20)  | 0.00 (± 21.63)  |  |  |  |
| Financial difficulties - Change at Cycle 31 (n=15)  | -2.22 (± 19.79) |  |  |  |
| Financial difficulties - Change at Cycle 33 (n=11)  | -3.03 (± 17.98) |  |  |  |
| Financial difficulties - Change at Cycle 35 (n=10)  | 0.00 (± 15.71)  |  |  |  |

|                                                   |                     |  |  |  |
|---------------------------------------------------|---------------------|--|--|--|
| Financial difficulties - Change at EOT<br>(n=337) | 2.97 ( $\pm$ 27.90) |  |  |  |
|---------------------------------------------------|---------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in HRQL EQ-5D-3L Quality of Life: Single Index Utility Score

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Change From Baseline in HRQL EQ-5D-3L Quality of Life: Single Index Utility Score |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

EQ-5D was a standardized HRQL questionnaire consisting of EQ-5D descriptive system and Visual Analogue Scale (VAS). EQ-5D descriptive system comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression measured on 3 levels (no problem, some problems & severe problems) within a particular EQ-5D dimension. 5 dimensional 3-level system was converted into single index utility score. Possible values for single index utility score ranged from -0.594 (severe problems in all dimensions) to 1.0 (no problem in all dimensions) on scale where 1 represented best possible health state. EQ-5D analysis population: subjects who signed informed consent form, had an evaluable EQ-5D questionnaire at baseline and at least one evaluable assessment post baseline and received at least part of one dose of study treatment (either Aflibercept or FOLFIRI). Here, 'n'=subjects analyzed at specified timepoints.

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

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

|                                      |                                                                    |  |  |  |
|--------------------------------------|--------------------------------------------------------------------|--|--|--|
| <b>End point values</b>              | Aflibercept +<br>FOLFIRI<br>(Irinotecan, 5-<br>FU &<br>Leucovorin) |  |  |  |
| Subject group type                   | Reporting group                                                    |  |  |  |
| Number of subjects analysed          | 623                                                                |  |  |  |
| Units: units on a scale              |                                                                    |  |  |  |
| arithmetic mean (standard deviation) |                                                                    |  |  |  |
| Baseline (n= 623)                    | 0.77 ( $\pm$ 0.24)                                                 |  |  |  |
| Change at Cycle 3 (n= 536)           | -0.02 ( $\pm$ 0.23)                                                |  |  |  |
| Change at Cycle 5 (n= 428)           | -0.03 ( $\pm$ 0.22)                                                |  |  |  |
| Change at Cycle 7 (n= 335)           | -0.04 ( $\pm$ 0.23)                                                |  |  |  |
| Change at Cycle 9 (n= 269)           | -0.05 ( $\pm$ 0.24)                                                |  |  |  |
| Change at Cycle 11 (n= 226)          | -0.07 ( $\pm$ 0.25)                                                |  |  |  |
| Change at Cycle 13 (n= 149)          | -0.05 ( $\pm$ 0.20)                                                |  |  |  |
| Change at Cycle 15 (n= 119)          | -0.06 ( $\pm$ 0.23)                                                |  |  |  |
| Change at Cycle 17 (n= 81)           | -0.05 ( $\pm$ 0.24)                                                |  |  |  |
| Change at Cycle 19 (n= 58)           | -0.05 ( $\pm$ 0.18)                                                |  |  |  |
| Change at Cycle 21 (n= 44)           | -0.09 ( $\pm$ 0.20)                                                |  |  |  |
| Change at Cycle 23 (n= 34)           | -0.14 ( $\pm$ 0.26)                                                |  |  |  |
| Change at Cycle 25 (n= 28)           | -0.08 ( $\pm$ 0.21)                                                |  |  |  |
| Change at Cycle 27 (n= 23)           | -0.08 ( $\pm$ 0.21)                                                |  |  |  |

|                            |                |  |  |  |
|----------------------------|----------------|--|--|--|
| Change at Cycle 29 (n= 20) | -0.08 (± 0.20) |  |  |  |
| Change at Cycle 31 (n= 15) | -0.12 (± 0.30) |  |  |  |
| Change at Cycle 33 (n= 11) | 0.02 (± 0.14)  |  |  |  |
| Change at Cycle 35 (n= 10) | -0.05 (± 0.14) |  |  |  |
| Change at EOT (n= 343)     | -0.11 (± 0.30) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in HRQL EQ-5D-3L VAS Score

|                 |                                                 |
|-----------------|-------------------------------------------------|
| End point title | Change From Baseline in HRQL EQ-5D-3L VAS Score |
|-----------------|-------------------------------------------------|

End point description:

EQ-5D was a standardized HRQL questionnaire consisting of EQ-5D descriptive system and VAS. EQ-5D descriptive system comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression measured on 3 levels (no problem, some problems & severe problems) within a particular EQ-5D dimension. 5 dimensional 3-level system was converted into single index utility score. The VAS recorded the respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. EQ-5D analysis population. Here, 'n'=subjects analysed at specified time points.

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

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

|                                      |                                                       |  |  |  |
|--------------------------------------|-------------------------------------------------------|--|--|--|
| <b>End point values</b>              | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |  |
| Subject group type                   | Reporting group                                       |  |  |  |
| Number of subjects analysed          | 623                                                   |  |  |  |
| Units: units on a scale              |                                                       |  |  |  |
| arithmetic mean (standard deviation) |                                                       |  |  |  |
| Baseline (n= 577)                    | 72.81 (± 18.28)                                       |  |  |  |
| Change at Cycle 3 (n= 482)           | -1.85 (± 15.35)                                       |  |  |  |
| Change at Cycle 5 (n= 381)           | -2.15 (± 14.31)                                       |  |  |  |
| Change at Cycle 7 (n= 303)           | -2.20 (± 16.33)                                       |  |  |  |
| Change at Cycle 9 (n= 236)           | -2.74 (± 14.28)                                       |  |  |  |
| Change at Cycle 11 (n= 203)          | -3.10 (± 14.40)                                       |  |  |  |
| Change at Cycle 13 (n= 134)          | -2.36 (± 15.29)                                       |  |  |  |
| Change at Cycle 15 (n= 103)          | -1.05 (± 15.51)                                       |  |  |  |

|                            |                 |  |  |  |
|----------------------------|-----------------|--|--|--|
| Change at Cycle 17 (n= 74) | -1.91 (± 13.54) |  |  |  |
| Change at Cycle 19 (n= 52) | -3.06 (± 13.85) |  |  |  |
| Change at Cycle 21 (n= 38) | -2.13 (± 14.98) |  |  |  |
| Change at Cycle 23 (n= 30) | -5.77 (± 13.50) |  |  |  |
| Change at Cycle 25 (n= 25) | -7.28 (± 10.53) |  |  |  |
| Change at Cycle 27 (n= 17) | -4.94 (± 8.68)  |  |  |  |
| Change at Cycle 29 (n= 15) | -8.80 (± 10.12) |  |  |  |
| Change at Cycle 31 (n= 13) | -6.69 (± 12.61) |  |  |  |
| Change at Cycle 33 (n= 10) | -7.90 (± 13.08) |  |  |  |
| Change at Cycle 35 (n= 8)  | -8.88 (± 11.53) |  |  |  |
| Change at EOT (n= 310)     | -6.67 (± 17.38) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the final visit (214 weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during 'on-treatment period' (from the first dose of treatment to 30 days after the last dose of treatment [either aflibercept or FOLFIRI]). Analysis was performed on safety population.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.0   |

### Reporting groups

|                       |                                                       |
|-----------------------|-------------------------------------------------------|
| Reporting group title | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |
|-----------------------|-------------------------------------------------------|

Reporting group description:

Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m<sup>2</sup> IV infusion over 90 minutes and Leucovorin 400 mg/m<sup>2</sup> IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m<sup>2</sup> IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m<sup>2</sup> continuous IV infusion over 46 hours on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment.

| Serious adverse events                                              | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |
|---------------------------------------------------------------------|-------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                                       |  |  |
| subjects affected / exposed                                         | 272 / 779 (34.92%)                                    |  |  |
| number of deaths (all causes)                                       | 48                                                    |  |  |
| number of deaths resulting from adverse events                      |                                                       |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                       |  |  |
| Metastases To Central Nervous System                                |                                                       |  |  |
| subjects affected / exposed                                         | 1 / 779 (0.13%)                                       |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                 |  |  |
| Cancer Pain                                                         |                                                       |  |  |
| subjects affected / exposed                                         | 1 / 779 (0.13%)                                       |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                 |  |  |
| Tumour Associated Fever                                             |                                                       |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular disorders                              |                  |  |  |
| Deep Vein Thrombosis                            |                  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypertension                                    |                  |  |  |
| subjects affected / exposed                     | 11 / 779 (1.41%) |  |  |
| occurrences causally related to treatment / all | 10 / 13          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypotension                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Orthostatic Hypotension                         |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral Ischaemia                            |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vena Cava Thrombosis                            |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Surgical and medical procedures                 |                  |  |  |
| Cancer Surgery                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| General disorders and administration            |                  |  |  |



|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| site conditions                                 |                  |  |  |  |
| Asthenia                                        |                  |  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Chest Pain                                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fatigue                                         |                  |  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Disease Progression                             |                  |  |  |  |
| subjects affected / exposed                     | 23 / 779 (2.95%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 23           |  |  |  |
| deaths causally related to treatment / all      | 0 / 19           |  |  |  |
| General Physical Health Deterioration           |                  |  |  |  |
| subjects affected / exposed                     | 5 / 779 (0.64%)  |  |  |  |
| occurrences causally related to treatment / all | 3 / 5            |  |  |  |
| deaths causally related to treatment / all      | 2 / 2            |  |  |  |
| Malaise                                         |                  |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Multiple Organ Dysfunction Syndrome             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Pain                                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| Pyrexia                                         |                  |  |  |
| subjects affected / exposed                     | 12 / 779 (1.54%) |  |  |
| occurrences causally related to treatment / all | 6 / 18           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sudden Death                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Immune system disorders                         |                  |  |  |
| Anaphylactic Shock                              |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Acute Pulmonary Oedema                          |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 1 / 2            |  |  |
| Atelectasis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cough                                           |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dyspnoea                                        |                  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 1 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemoptysis                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Hiccups                                         |                 |  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pleural Effusion                                |                 |  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pneumonia Aspiration                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pneumonitis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumothorax                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary Embolism                              |                 |  |  |  |
| subjects affected / exposed                     | 9 / 779 (1.16%) |  |  |  |
| occurrences causally related to treatment / all | 9 / 9           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary Haemorrhage                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |  |
| Respiratory Failure                             |                 |  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Thoracic Haemorrhage                            |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Confusional State                               |                 |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Investigations                                  |                 |  |  |
| Alanine Aminotransferase Increased              |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Accidental Exposure To Product                  |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Accidental Overdose                             |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anastomotic Leak                                |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Contrast Media Reaction                         |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hip Fracture                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Gastrointestinal Stoma Complication             |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Meniscus Injury                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Stoma Site Haemorrhage                          |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute Myocardial Infarction                     |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial Fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina Pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial Thrombosis                               |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial Flutter                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac Failure                                 |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac Failure Congestive                      |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardio-Respiratory Arrest                       |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Coronary Artery Thrombosis                      |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Supraventricular Tachycardia                    |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ventricular Tachycardia                         |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Encephalopathy                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Generalised Tonic-Clonic Seizure                |                 |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Headache                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paraparesis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Posterior Reversible Encephalopathy Syndrome    |                  |  |  |
| subjects affected / exposed                     | 3 / 779 (0.39%)  |  |  |
| occurrences causally related to treatment / all | 3 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subarachnoid Haemorrhage                        |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| White Matter Lesion                             |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood and lymphatic system disorders            |                  |  |  |
| Anaemia                                         |                  |  |  |
| subjects affected / exposed                     | 7 / 779 (0.90%)  |  |  |
| occurrences causally related to treatment / all | 4 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Febrile Neutropenia                             |                  |  |  |
| subjects affected / exposed                     | 12 / 779 (1.54%) |  |  |
| occurrences causally related to treatment / all | 12 / 12          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neutropenia                                     |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 14 / 779 (1.80%) |  |  |
| occurrences causally related to treatment / all | 17 / 18          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombocytopenia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombotic Microangiopathy                      |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Eye disorders                                   |                  |  |  |
| Retinal Detachment                              |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |
| Abdominal Pain                                  |                  |  |  |
| subjects affected / exposed                     | 8 / 779 (1.03%)  |  |  |
| occurrences causally related to treatment / all | 2 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal Pain Upper                            |                  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal Fissure                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal Fistula                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anorectal Ulcer                                 |                  |  |  |



|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ascites                                         |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colitis                                         |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Constipation                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diarrhoea                                       |                  |  |  |
| subjects affected / exposed                     | 39 / 779 (5.01%) |  |  |
| occurrences causally related to treatment / all | 42 / 43          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Duodenal Ulcer Haemorrhage                      |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enteritis                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enterocutaneous Fistula                         |                  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enterovesical Fistula                           |                  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Faecaloma                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fistula Of Small Intestine                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal Fistula                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal Haemorrhage                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal Hypomotility                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal Perforation                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gingival Bleeding                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Haematemesis                                    |                 |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhoids                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhoids Thrombosed                         |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileus                                           |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileus Paralytic                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Inguinal Hernia                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal Obstruction                          |                  |  |  |
| subjects affected / exposed                     | 12 / 779 (1.54%) |  |  |
| occurrences causally related to treatment / all | 0 / 13           |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Intestinal Perforation                          |                  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Large Intestine Perforation                     |                  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 4 / 779 (0.51%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |  |
| Lower Gastrointestinal Haemorrhage              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Melaena                                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Nausea                                          |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Odynophagia                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oesophagitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Proctalgia                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Proctitis                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rectal Haemorrhage                              |                 |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rectal Perforation                              |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rectal Tenesmus                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stomatitis                                      |                  |  |  |
| subjects affected / exposed                     | 9 / 779 (1.16%)  |  |  |
| occurrences causally related to treatment / all | 9 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small Intestinal Obstruction                    |                  |  |  |
| subjects affected / exposed                     | 4 / 779 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Subileus                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vomiting                                        |                  |  |  |
| subjects affected / exposed                     | 10 / 779 (1.28%) |  |  |
| occurrences causally related to treatment / all | 8 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatobiliary disorders                         |                  |  |  |
| Cholangitis                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cholecystitis                                   |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis Acute                             |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholestasis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic Failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Jaundice Cholestatic                            |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Portal Hypertension                             |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| 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                     | 3 / 779 (0.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Hydronephrosis                                  |                 |  |  |

|                                                        |                 |  |  |
|--------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                            | 3 / 779 (0.39%) |  |  |
| occurrences causally related to treatment / all        | 0 / 3           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Nephrotic Syndrome</b>                              |                 |  |  |
| subjects affected / exposed                            | 5 / 779 (0.64%) |  |  |
| occurrences causally related to treatment / all        | 5 / 5           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Prerenal Failure</b>                                |                 |  |  |
| subjects affected / exposed                            | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Urinary Retention</b>                               |                 |  |  |
| subjects affected / exposed                            | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Proteinuria</b>                                     |                 |  |  |
| subjects affected / exposed                            | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all        | 2 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| <b>Back Pain</b>                                       |                 |  |  |
| subjects affected / exposed                            | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal Chest Pain</b>                      |                 |  |  |
| subjects affected / exposed                            | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal Pain</b>                            |                 |  |  |
| subjects affected / exposed                            | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Neck Pain</b>                                       |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Infections and infestations</b>              |                 |  |  |
| <b>Abdominal Abscess</b>                        |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Abdominal Infection</b>                      |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Abdominal Wall Abscess</b>                   |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Bronchitis</b>                               |                 |  |  |
| subjects affected / exposed                     | 3 / 779 (0.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Catheter Site Abscess</b>                    |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Device Related Infection</b>                 |                 |  |  |
| subjects affected / exposed                     | 7 / 779 (0.90%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| <b>Diabetic Foot Infection</b>                  |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Escherichia Urinary Tract Infection</b>      |                 |  |  |



|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Febrile Infection                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis Escherichia Coli                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Herpes Zoster                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Herpes Zoster Meningoencephalitis               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infection                                       |                 |  |  |  |
| subjects affected / exposed                     | 5 / 779 (0.64%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 5           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infective Myositis                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Klebsiella Infection                            |                 |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Localised Infection                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower Respiratory Tract Infection               |                 |  |  |  |
| subjects affected / exposed                     | 3 / 779 (0.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung Infection                                  |                 |  |  |  |
| subjects affected / exposed                     | 3 / 779 (0.39%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Neutropenic Infection                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Neutropenic Sepsis                              |                 |  |  |  |
| subjects affected / exposed                     | 3 / 779 (0.39%) |  |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |  |
| deaths causally related to treatment / all      | 2 / 2           |  |  |  |
| Parainfluenzae Virus Infection                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pelvic Abscess                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Periodontitis                                   |                 |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pharyngitis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Phlebitis Infective                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 8 / 779 (1.03%) |  |  |  |
| occurrences causally related to treatment / all | 3 / 8           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pyelonephritis                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rectal Abscess                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Respiratory Tract Infection                     |                 |  |  |  |
| subjects affected / exposed                     | 3 / 779 (0.39%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis                                          |                 |  |  |  |
| subjects affected / exposed                     | 7 / 779 (0.90%) |  |  |  |
| occurrences causally related to treatment / all | 6 / 8           |  |  |  |
| deaths causally related to treatment / all      | 2 / 2           |  |  |  |
| Septic Shock                                    |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 1 / 2           |  |  |
| Sinusitis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Streptococcal Bacteraemia                       |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tracheobronchitis                               |                 |  |  |
| subjects affected / exposed                     | 2 / 779 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tuberculosis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper Respiratory Tract Infection               |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary Tract Infection                         |                 |  |  |
| subjects affected / exposed                     | 5 / 779 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urosepsis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Decreased Appetite                              |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 5 / 779 (0.64%) |  |  |
| occurrences causally related to treatment / all | 4 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypercalcaemia                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 779 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin) |  |  |
|-------------------------------------------------------|-------------------------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                                       |  |  |
| subjects affected / exposed                           | 744 / 779 (95.51%)                                    |  |  |
| Investigations                                        |                                                       |  |  |
| Weight Decreased                                      |                                                       |  |  |
| subjects affected / exposed                           | 171 / 779 (21.95%)                                    |  |  |
| occurrences (all)                                     | 185                                                   |  |  |
| Vascular disorders                                    |                                                       |  |  |
| Hypertension                                          |                                                       |  |  |
| subjects affected / exposed                           | 369 / 779 (47.37%)                                    |  |  |
| occurrences (all)                                     | 557                                                   |  |  |
| Nervous system disorders                              |                                                       |  |  |
| Headache                                              |                                                       |  |  |
| subjects affected / exposed                           | 105 / 779 (13.48%)                                    |  |  |
| occurrences (all)                                     | 133                                                   |  |  |
| Blood and lymphatic system disorders                  |                                                       |  |  |

|                                                                          |                            |  |  |
|--------------------------------------------------------------------------|----------------------------|--|--|
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)          | 277 / 779 (35.56%)<br>611  |  |  |
| General disorders and administration site conditions                     |                            |  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)             | 192 / 779 (24.65%)<br>318  |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)              | 283 / 779 (36.33%)<br>415  |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 87 / 779 (11.17%)<br>112   |  |  |
| Gastrointestinal disorders                                               |                            |  |  |
| Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)       | 150 / 779 (19.26%)<br>194  |  |  |
| Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all) | 67 / 779 (8.60%)<br>77     |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 148 / 779 (19.00%)<br>180  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 464 / 779 (59.56%)<br>1000 |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 337 / 779 (43.26%)<br>640  |  |  |
| Proctalgia<br>subjects affected / exposed<br>occurrences (all)           | 39 / 779 (5.01%)<br>44     |  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 329 / 779 (42.23%)<br>570  |  |  |
| Vomiting                                                                 |                            |  |  |

|                                                 |                    |  |  |
|-------------------------------------------------|--------------------|--|--|
| subjects affected / exposed                     | 190 / 779 (24.39%) |  |  |
| occurrences (all)                               | 311                |  |  |
| Respiratory, thoracic and mediastinal disorders |                    |  |  |
| Cough                                           |                    |  |  |
| subjects affected / exposed                     | 57 / 779 (7.32%)   |  |  |
| occurrences (all)                               | 65                 |  |  |
| Dysphonia                                       |                    |  |  |
| subjects affected / exposed                     | 131 / 779 (16.82%) |  |  |
| occurrences (all)                               | 153                |  |  |
| Dyspnoea                                        |                    |  |  |
| subjects affected / exposed                     | 62 / 779 (7.96%)   |  |  |
| occurrences (all)                               | 69                 |  |  |
| Epistaxis                                       |                    |  |  |
| subjects affected / exposed                     | 153 / 779 (19.64%) |  |  |
| occurrences (all)                               | 193                |  |  |
| Skin and subcutaneous tissue disorders          |                    |  |  |
| Alopecia                                        |                    |  |  |
| subjects affected / exposed                     | 143 / 779 (18.36%) |  |  |
| occurrences (all)                               | 144                |  |  |
| Palmar-Plantar Erythrodysaesthesia Syndrome     |                    |  |  |
| subjects affected / exposed                     | 79 / 779 (10.14%)  |  |  |
| occurrences (all)                               | 89                 |  |  |
| Renal and urinary disorders                     |                    |  |  |
| Proteinuria                                     |                    |  |  |
| subjects affected / exposed                     | 102 / 779 (13.09%) |  |  |
| occurrences (all)                               | 133                |  |  |
| Psychiatric disorders                           |                    |  |  |
| Insomnia                                        |                    |  |  |
| subjects affected / exposed                     | 54 / 779 (6.93%)   |  |  |
| occurrences (all)                               | 61                 |  |  |
| Musculoskeletal and connective tissue disorders |                    |  |  |
| Back Pain                                       |                    |  |  |
| subjects affected / exposed                     | 47 / 779 (6.03%)   |  |  |
| occurrences (all)                               | 50                 |  |  |
| Metabolism and nutrition disorders              |                    |  |  |

|                                                                        |                           |  |  |
|------------------------------------------------------------------------|---------------------------|--|--|
| Decreased Appetite<br>subjects affected / exposed<br>occurrences (all) | 206 / 779 (26.44%)<br>263 |  |  |
|------------------------------------------------------------------------|---------------------------|--|--|



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported