



## Clinical trial results:

**A single arm study in metastatic colorectal cancer patients treated with pharmacokinetically (PK) dose adjusted weekly or biweekly 5-fluorouracil (5-FU) regimes.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2011-003553-26    |
| Trial protocol           | DE                |
| Global end of trial date | 17 September 2014 |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 05 September 2018 |
| First version publication date | 05 September 2018 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | C-II-009 |
|-----------------------|----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                                       |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | CESAR Central European Society for Anticancer Drug Research-EWIV                                                      |
| Sponsor organisation address | Hanglössgasse, 4/1-3, Vienna, Austria, 1150                                                                           |
| Public contact               | Sponsor, CESAR Central European Society for Anticancer Drug Research-EWIV , 0043 1522309316, max.roessler@cesar.or.at |
| Scientific contact           | Sponsor, CESAR Central European Society for Anticancer Drug Research-EWIV , 0043 6765273814, max.roessler@cesar.or.at |

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                       | 03 December 2015  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 17 September 2014 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 17 September 2014 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To determine whether pharmacokinetically-guided dose adjustment of 5-FU provides a stable inpatient dose level of 20-30 mg.h /l. The primary analysis will be the comparison of the proportion of patients with AUC within 20 to 30 mg.h/L after the first 5-FU application versus the fourth application.

Protection of trial subjects:

Patients within this trial receive pharmacokinetically adapted 5-FU infusions. Beside the individual dose adaptation, which requires additional blood draws, patients are treated according to clinical routine. In order to further reduce interventions, the needle punctures required for PK-assessments were performed in course of routine blood draws.

Safety measures like regular blood analysis were performed according to clinical routine.

Background therapy:

n.a.

Evidence for comparator:

n.a.

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 13 July 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 | Germany: 75 |
| Worldwide total number of subjects   | 75          |
| EEA total number of subjects         | 75          |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 32 |
| From 65 to 84 years       | 43 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

7 study sites in Germany participated in the study. Recruitment started on 13.07.2012 and ended at 10.07.2014 as the last patient was recruited.

### Pre-assignment

Screening details:

The screening criteria were defined by the inclusion and exclusion criteria as defined in the study protocol.

### Period 1

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

Blinding implementation details:

n.a.

### Arms

|           |                            |
|-----------|----------------------------|
| Arm title | Experimental Treatment Arm |
|-----------|----------------------------|

Arm description:

Patients will be treated with AIO-regime (weekly), FUFOX-regime (weekly) or FOLFOX-6 regime (bi-weekly). Patients will be dosed for the first time in accordance to established local standard and then 5-FU will be individually adjusted before every chemotherapy application, beginning with the second application. Dose adjustments for 5-FU will be either calculated according to toxicity and/or to the results of plasma concentrations from the preceding application (see algorithm below). Patients will remain on study until a total of 6 doses of FU-treatment have been administered and the end-of-treatment visit has been performed (weekly regimen: 9 weeks and bi-weekly regimen 13 weeks) or until withdrawal of patient's consent, or withdrawal by the treating physician for safety reasons or due tumor progression, whatever comes first.

Following study completion, patients will receive further treatment according to best local practice.

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | 5-Fluoruracil                    |
| Investigational medicinal product code | L01BC02                          |
| Other name                             | 5-Fluor-1H-pyrimidin-2,4-dion    |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Administration according to SmPC. Individual dosing according to dosing algorithm outlined in CSP.

| Number of subjects in period 1 | Experimental Treatment Arm |
|--------------------------------|----------------------------|
| Started                        | 75                         |
| Completed                      | 75                         |



## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values                             | Overall trial | Total |  |
|----------------------------------------------------|---------------|-------|--|
| Number of subjects                                 | 75            | 75    |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero                                           |               | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) |               | 0     |  |
| Newborns (0-27 days)                               |               | 0     |  |
| Infants and toddlers (28 days-23 months)           |               | 0     |  |
| Children (2-11 years)                              |               | 0     |  |
| Adolescents (12-17 years)                          |               | 0     |  |
| Adults (18-64 years)                               |               | 0     |  |
| From 65-84 years                                   |               | 0     |  |
| 85 years and over                                  |               | 0     |  |
| Age continuous                                     |               |       |  |
| Age continuous                                     |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 65.06         |       |  |
| standard deviation                                 | ± 10.8        | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female                                             | 32            | 32    |  |
| Male                                               | 43            | 43    |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-AIO Week-2     |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP at week 2.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-FUFOX-Week2    |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP (FUFOX regime) at week 2.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-FOLFOX6 Week 3 |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP (FOLFOX-6 regime) at week 3.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                                                                                                                                                                                                                                                                |                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Subject analysis set title                                                                                                                                                                                                                                     | ITT-AIO Week-5     |
| Subject analysis set type                                                                                                                                                                                                                                      | Intention-to-treat |
| Subject analysis set description:                                                                                                                                                                                                                              |                    |
| Patient in the ITT group who received IMP at week 5.<br>The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.                   |                    |
| Subject analysis set title                                                                                                                                                                                                                                     | ITT-FUFOX-Week5    |
| Subject analysis set type                                                                                                                                                                                                                                      | Intention-to-treat |
| Subject analysis set description:                                                                                                                                                                                                                              |                    |
| Patient in the ITT group who received IMP (FUFOX regime) at week 5.<br>The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.    |                    |
| Subject analysis set title                                                                                                                                                                                                                                     | ITT-FOLFOX6 Week 9 |
| Subject analysis set type                                                                                                                                                                                                                                      | Intention-to-treat |
| Subject analysis set description:                                                                                                                                                                                                                              |                    |
| Patient in the ITT group who received IMP (FOLFOX-6 regime) at week 9.<br>The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis. |                    |

| Reporting group values                                                                                                                                                                                                                                    | ITT-AIO Week-2 | ITT-FUFOX-Week2 | ITT-FOLFOX6 Week 3 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-----------------|--------------------|
| Number of subjects                                                                                                                                                                                                                                        | 16             | 33              | 26                 |
| Age categorical                                                                                                                                                                                                                                           |                |                 |                    |
| Units: Subjects                                                                                                                                                                                                                                           |                |                 |                    |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                |                 |                    |
| Age continuous                                                                                                                                                                                                                                            |                |                 |                    |
| Age continuous                                                                                                                                                                                                                                            |                |                 |                    |
| Units: years                                                                                                                                                                                                                                              |                |                 |                    |
| arithmetic mean                                                                                                                                                                                                                                           | 71,77          | 60,84           | 66,29              |
| standard deviation                                                                                                                                                                                                                                        | ±              | ±               | ±                  |
| Gender categorical                                                                                                                                                                                                                                        |                |                 |                    |
| Units: Subjects                                                                                                                                                                                                                                           |                |                 |                    |
| Female                                                                                                                                                                                                                                                    | 32             |                 |                    |
| Male                                                                                                                                                                                                                                                      | 43             |                 |                    |

| Reporting group values                                                                                                             | ITT-AIO Week-5 | ITT-FUFOX-Week5 | ITT-FOLFOX6 Week 9 |
|------------------------------------------------------------------------------------------------------------------------------------|----------------|-----------------|--------------------|
| Number of subjects                                                                                                                 | 16             | 33              | 26                 |
| Age categorical                                                                                                                    |                |                 |                    |
| Units: Subjects                                                                                                                    |                |                 |                    |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months) |                |                 |                    |

|                           |       |       |       |
|---------------------------|-------|-------|-------|
| Children (2-11 years)     |       |       |       |
| Adolescents (12-17 years) |       |       |       |
| Adults (18-64 years)      |       |       |       |
| From 65-84 years          |       |       |       |
| 85 years and over         |       |       |       |
| Age continuous            |       |       |       |
| Age continuous            |       |       |       |
| Units: years              |       |       |       |
| arithmetic mean           | 71,77 | 60,84 | 66,29 |
| standard deviation        | ±     | ±     | ±     |
| Gender categorical        |       |       |       |
| Units: Subjects           |       |       |       |
| Female                    |       |       |       |
| Male                      |       |       |       |

## End points

### End points reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Experimental Treatment Arm |
|-----------------------|----------------------------|

Reporting group description:

Patients will be treated with AIO-regime (weekly), FUFOX-regime (weekly) or FOLFOX-6 regime (bi-weekly). Patients will be dosed for the first time in accordance to established local standard and then 5-FU will be individually adjusted before every chemotherapy application, beginning with the second application. Dose adjustments for 5-FU will be either calculated according to toxicity and/or to the results of plasma concentrations from the preceding application (see algorithm below). Patients will remain on study until a total of 6 doses of FU-treatment have been administered and the end-of-treatment visit has been performed (weekly regimen: 9 weeks and bi-weekly regimen 13 weeks) or until withdrawal of patient's consent, or withdrawal by the treating physician for safety reasons or due tumor progression, whatever comes first.

Following study completion, patients will receive further treatment according to best local practice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-AIO Week-2     |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP at week 2.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-FUFOX-Week2    |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP (FUFOX regime) at week 2.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-FOLFOX6 Week 3 |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP (FOLFOX-6 regime) at week 3.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-AIO Week-5     |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP at week 5.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-FUFOX-Week5    |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP (FUFOX regime) at week 5.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT-FOLFOX6 Week 9 |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Patient in the ITT group who received IMP (FOLFOX-6 regime) at week 9.

The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

**Primary: Primary Endpoint in AIO ITT Patients**

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Primary Endpoint in AIO ITT Patients |
|-----------------|--------------------------------------|

End point description:

To determine whether pharmacokinetically-guided dose adjustment of 5-FU provides a stable inpatient dose level of 20-30 mg.h /l. The primary analysis will be the comparison of the proportion of patients with AUC within 20 to 30 mg.h/L after the first 5-FU application versus the fourth application.

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

End point timeframe:

First 5-FU application till fourth 5 FU application

| End point values            | Experimental Treatment Arm | ITT-AIO Week-2       | ITT-AIO Week-5       |  |
|-----------------------------|----------------------------|----------------------|----------------------|--|
| Subject group type          | Reporting group            | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed | 16                         | 16                   | 16                   |  |
| Units: Patients             | 16                         | 16                   | 16                   |  |

**Statistical analyses**

|                            |                |
|----------------------------|----------------|
| Statistical analysis title | McNemar's test |
|----------------------------|----------------|

Statistical analysis description:

The primary endpoint was the comparison between the proportion of patients with an AUC in target range during the first 5-FU application versus the fourth 5-FU application.

This comparison was performed with a McNemar's test to determine whether the row and column marginal frequencies (in a 2x2 contingency table of the first vs. fourth application vs. within target range vs. not within target range) were equal.

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Comparison groups                       | ITT-AIO Week-2 v ITT-AIO Week-5 |
| Number of subjects included in analysis | 32                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other <sup>[1]</sup>            |
| P-value                                 | = 0.5637                        |
| Method                                  | McNemar                         |

Notes:

[1] - McNemar's test to determine whether the row and column marginal frequencies (in a 2x2 contingency table of the first vs. fourth application vs. within target range vs. not within target range) were equal.

**Primary: Primary Endpoint in FUFOX ITT Patients**

|                 |                                        |
|-----------------|----------------------------------------|
| End point title | Primary Endpoint in FUFOX ITT Patients |
|-----------------|----------------------------------------|

End point description:

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

End point timeframe:

Between 1st and Fourth study drug administration

| End point values            | ITT-FUFOX-Week2      | ITT-FUFOX-Week5      |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 33                   | 33                   |  |  |
| Units: Patients             | 28                   | 27                   |  |  |

### Statistical analyses

| Statistical analysis title              | McNemar's test                    |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | ITT-FUFOX-Week2 v ITT-FUFOX-Week5 |
| Number of subjects included in analysis | 66                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           |                                   |
| P-value                                 | = 0.1336                          |
| Method                                  | McNemar                           |

### Primary: Primary Endpoint in FOLFOX-6 ITT Patients

|                             |                                           |
|-----------------------------|-------------------------------------------|
| End point title             | Primary Endpoint in FOLFOX-6 ITT Patients |
| End point description:      |                                           |
| End point type              | Primary                                   |
| End point timeframe:        |                                           |
| First to fourth application |                                           |

| End point values            | ITT-FOLFOX6 Week 3   | ITT-FOLFOX6 Week 9   |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 26                   | 26                   |  |  |
| Units: Patients             | 24                   | 22                   |  |  |

### Statistical analyses

| Statistical analysis title              | McNemar's test                          |
|-----------------------------------------|-----------------------------------------|
| Comparison groups                       | ITT-FOLFOX6 Week 9 v ITT-FOLFOX6 Week 3 |
| Number of subjects included in analysis | 52                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other <sup>[2]</sup>                    |
| P-value                                 | = 0.0209                                |
| Method                                  | McNemar                                 |

Notes:

[2] - McNemar's test

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs have been assessed from first study drug administration to the End of treatment visit.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

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

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | AIO (weekly) |
|-----------------------|--------------|

Reporting group description:

AIO-Regimen:

5-FU 2600 mg/m<sup>2</sup>. Infusion for 24 hours. Leucovorin 200 mg/m<sup>2</sup>

Once weekly for 6 weeks, 2 weeks off.

Continuous intravenous infusion of 5-FU for 24 hours given as a continuous infusion. Additionally the regimen can contain oxaliplatin.

Either bevacizumab or cetuximab may be added to the regimens, according to local medical practice at each center.

|                       |                |
|-----------------------|----------------|
| Reporting group title | FUFOX (weekly) |
|-----------------------|----------------|

Reporting group description:

FUFOX:

Oxaliplatin 60mg/m<sup>2</sup>. Infusion for 2 (-6) hours.

5FU 2000 mg/m<sup>2</sup>. Infusion for 24 hours. Leucovorin 200 mg/m<sup>2</sup>

Once weekly for 6 weeks, 2 weeks off

Continuous intravenous infusion of 5-FU for 24 hours given as a continuous infusion. Additionally the regimen can contain oxaliplatin.

Either bevacizumab or cetuximab may be added to the regimens, according to local medical practice at each center.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | FOLFOX6 (bi-weekly) |
|-----------------------|---------------------|

Reporting group description:

Modified FOLFOX6:

Oxaliplatin 85 mg/m<sup>2</sup> as Infusion for 2 (-6) hours.

5-FU 400 mg/m<sup>2</sup> on day 1 as bolus (OPTIONAL)

5-FU 2400 mg/m<sup>2</sup> Infusion for 46 hours.

Leucovorin 400 mg or 400mg/m<sup>2</sup> (the same dosing scheme should consistently be used for a patient)

Repeat every 2 weeks.

Either bevacizumab or cetuximab may be added to the regimen, according to local medical practice at each center.

| Serious adverse events                            | AIO (weekly)    | FUFOX (weekly)   | FOLFOX6 (bi-weekly) |
|---------------------------------------------------|-----------------|------------------|---------------------|
| Total subjects affected by serious adverse events |                 |                  |                     |
| subjects affected / exposed                       | 4 / 16 (25.00%) | 13 / 33 (39.39%) | 5 / 26 (19.23%)     |
| number of deaths (all causes)                     | 2               | 1                | 1                   |
| number of deaths resulting from adverse events    | 2               | 1                | 1                   |
| Blood and lymphatic system disorders              |                 |                  |                     |
| Febrile neutropenia                               |                 |                  |                     |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Abdominal pain                                       |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General physical health deterioration                |                |                |                |
| subjects affected / exposed                          | 1 / 16 (6.25%) | 0 / 33 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 0          |
| Device dislocation                                   |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                        |                |                |                |
| Ulcerative keratitis                                 |                |                |                |
| subjects affected / exposed                          | 1 / 16 (6.25%) | 0 / 33 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                           |                |                |                |
| Abdominal adhesions                                  |                |                |                |
| subjects affected / exposed                          | 1 / 16 (6.25%) | 0 / 33 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain upper                                 |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Constipation                                         |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                 |                |
|-------------------------------------------------|----------------|-----------------|----------------|
| Diarrhoea                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 5 / 33 (15.15%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 5 / 5           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 33 (6.06%)  | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Ileus                                           |                |                 |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 33 (0.00%)  | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Ileus paralytic                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Intestinal fistula                              |                |                 |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 33 (0.00%)  | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Large intestine perforation                     |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Nausea                                          |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Subileus                                        |                |                 |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 33 (3.03%)  | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| Vomiting                                        |                |                 |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 3 / 33 (9.09%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Liver disorder                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Urticaria                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal failure                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Abscess                                         |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Candida sepsis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Escherichia infection                           |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal infection                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peritonitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis                                          |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 33 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Septic encephalopathy                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 3 / 33 (9.09%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Hyponatraemia                                   |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 33 (3.03%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                           | AIO (weekly)     | FUFOX (weekly)   | FOLFOX6 (bi-weekly) |
|-------------------------------------------------------------|------------------|------------------|---------------------|
| Total subjects affected by non-serious adverse events       |                  |                  |                     |
| subjects affected / exposed                                 | 14 / 16 (87.50%) | 32 / 33 (96.97%) | 26 / 26 (100.00%)   |
| <b>Vascular disorders</b>                                   |                  |                  |                     |
| Hypotension                                                 |                  |                  |                     |
| subjects affected / exposed                                 | 0 / 16 (0.00%)   | 0 / 33 (0.00%)   | 1 / 26 (3.85%)      |
| occurrences (all)                                           | 0                | 0                | 1                   |
| Phlebitis                                                   |                  |                  |                     |
| subjects affected / exposed                                 | 0 / 16 (0.00%)   | 0 / 33 (0.00%)   | 2 / 26 (7.69%)      |
| occurrences (all)                                           | 0                | 0                | 2                   |
| Thrombosis                                                  |                  |                  |                     |
| subjects affected / exposed                                 | 0 / 16 (0.00%)   | 1 / 33 (3.03%)   | 0 / 26 (0.00%)      |
| occurrences (all)                                           | 0                | 1                | 0                   |
| Venous thrombosis                                           |                  |                  |                     |
| subjects affected / exposed                                 | 0 / 16 (0.00%)   | 1 / 33 (3.03%)   | 0 / 26 (0.00%)      |
| occurrences (all)                                           | 0                | 1                | 0                   |
| <b>General disorders and administration site conditions</b> |                  |                  |                     |
| Asthenia                                                    |                  |                  |                     |
| subjects affected / exposed                                 | 1 / 16 (6.25%)   | 3 / 33 (9.09%)   | 1 / 26 (3.85%)      |
| occurrences (all)                                           | 1                | 3                | 1                   |
| Catheter site pain                                          |                  |                  |                     |
| subjects affected / exposed                                 | 0 / 16 (0.00%)   | 1 / 33 (3.03%)   | 1 / 26 (3.85%)      |
| occurrences (all)                                           | 0                | 1                | 1                   |
| Chest discomfort                                            |                  |                  |                     |
| subjects affected / exposed                                 | 1 / 16 (6.25%)   | 0 / 33 (0.00%)   | 0 / 26 (0.00%)      |
| occurrences (all)                                           | 1                | 0                | 0                   |
| Chest pain                                                  |                  |                  |                     |
| subjects affected / exposed                                 | 0 / 16 (0.00%)   | 0 / 33 (0.00%)   | 1 / 26 (3.85%)      |
| occurrences (all)                                           | 0                | 0                | 1                   |
| Chills                                                      |                  |                  |                     |
| subjects affected / exposed                                 | 1 / 16 (6.25%)   | 2 / 33 (6.06%)   | 1 / 26 (3.85%)      |
| occurrences (all)                                           | 1                | 2                | 1                   |
| Discomfort                                                  |                  |                  |                     |

|                                       |                 |                  |                 |
|---------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed           | 0 / 16 (0.00%)  | 1 / 33 (3.03%)   | 0 / 26 (0.00%)  |
| occurrences (all)                     | 0               | 1                | 0               |
| Fatigue                               |                 |                  |                 |
| subjects affected / exposed           | 4 / 16 (25.00%) | 10 / 33 (30.30%) | 9 / 26 (34.62%) |
| occurrences (all)                     | 4               | 10               | 9               |
| Mucosal dryness                       |                 |                  |                 |
| subjects affected / exposed           | 1 / 16 (6.25%)  | 1 / 33 (3.03%)   | 0 / 26 (0.00%)  |
| occurrences (all)                     | 1               | 1                | 0               |
| General physical health deterioration |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)                     | 0               | 0                | 1               |
| Impaired healing                      |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)                     | 0               | 0                | 1               |
| Influenza like illness                |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)                     | 0               | 0                | 1               |
| Mucosal inflammation                  |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 2 / 33 (6.06%)   | 5 / 26 (19.23%) |
| occurrences (all)                     | 0               | 2                | 5               |
| Needle issue                          |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)                     | 0               | 0                | 1               |
| Oedema                                |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 1 / 33 (3.03%)   | 0 / 26 (0.00%)  |
| occurrences (all)                     | 0               | 1                | 0               |
| Oedema peripheral                     |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)                     | 0               | 0                | 1               |
| Pyrexia                               |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 4 / 33 (12.12%)  | 5 / 26 (19.23%) |
| occurrences (all)                     | 0               | 4                | 6               |
| Swelling                              |                 |                  |                 |
| subjects affected / exposed           | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)                     | 0               | 0                | 1               |
| Temperature intolerance               |                 |                  |                 |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |
| Immune system disorders                          |                     |                     |                     |
| Hypersensitivity                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 0 / 33 (0.00%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 0                   | 0                   | 2                   |
| Drug hypersensitivity                            |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 33 (0.00%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 1                   | 0                   | 2                   |
| Respiratory, thoracic and mediastinal disorders  |                     |                     |                     |
| Cough                                            |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 33 (0.00%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 1                   | 0                   | 2                   |
| Dyspnoea                                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 2 / 33 (6.06%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 0                   | 2                   | 1                   |
| Epistaxis                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 33 (3.03%)      | 5 / 26 (19.23%)     |
| occurrences (all)                                | 0                   | 1                   | 5                   |
| Oropharyngeal pain                               |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 33 (0.00%)      | 0 / 26 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Productive cough                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 33 (3.03%)      | 0 / 26 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Pulmonary embolism                               |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 0 / 33 (0.00%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Psychiatric disorders                            |                     |                     |                     |
| Agitation                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 0 / 33 (0.00%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Depression                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 33 (3.03%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 0                   | 1                   | 1                   |
| Sleep disorder                                   |                     |                     |                     |

|                                                                                           |                     |                     |                     |
|-------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                          | 0 / 16 (0.00%)<br>0 | 1 / 33 (3.03%)<br>1 | 0 / 26 (0.00%)<br>0 |
| Investigations                                                                            |                     |                     |                     |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)    | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0 | 2 / 26 (7.69%)<br>2 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 1 / 33 (3.03%)<br>1 | 1 / 26 (3.85%)<br>1 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |
| Blood magnesium increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0 | 2 / 26 (7.69%)<br>2 |
| Blood urine present<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 16 (6.25%)<br>1 | 0 / 33 (0.00%)<br>0 | 0 / 26 (0.00%)<br>0 |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 16 (0.00%)<br>0 | 1 / 33 (3.03%)<br>1 | 0 / 26 (0.00%)<br>0 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 16 (0.00%)<br>0 | 1 / 33 (3.03%)<br>1 | 0 / 26 (0.00%)<br>0 |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |
| Protein total decreased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 16 (0.00%)<br>0 | 2 / 33 (6.06%)<br>2 | 0 / 26 (0.00%)<br>0 |
| White blood cell count decreased                                                          |                     |                     |                     |

|                                                                                                                                   |                     |                      |                      |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                                  | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0  | 3 / 26 (11.54%)<br>3 |
| Injury, poisoning and procedural complications<br>Post procedural haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1 | 0 / 33 (0.00%)<br>0  | 0 / 26 (0.00%)<br>0  |
| Cardiac disorders<br>Cardiovascular disorder<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 16 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0  | 1 / 26 (3.85%)<br>1  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                                                   | 1 / 16 (6.25%)<br>1 | 0 / 33 (0.00%)<br>0  | 2 / 26 (7.69%)<br>2  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 16 (0.00%)<br>0 | 1 / 33 (3.03%)<br>1  | 1 / 26 (3.85%)<br>1  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                                                     | 1 / 16 (6.25%)<br>1 | 1 / 33 (3.03%)<br>1  | 2 / 26 (7.69%)<br>2  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                                      | 1 / 16 (6.25%)<br>1 | 1 / 33 (3.03%)<br>1  | 3 / 26 (11.54%)<br>3 |
| Mononeuropathy<br>subjects affected / exposed<br>occurrences (all)                                                                | 0 / 16 (0.00%)<br>0 | 1 / 33 (3.03%)<br>1  | 0 / 26 (0.00%)<br>0  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                                                         | 0 / 16 (0.00%)<br>0 | 2 / 33 (6.06%)<br>2  | 0 / 26 (0.00%)<br>0  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                                                  | 0 / 16 (0.00%)<br>0 | 9 / 33 (27.27%)<br>9 | 5 / 26 (19.23%)<br>5 |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 16 (0.00%)<br>0 | 6 / 33 (18.18%)<br>6 | 4 / 26 (15.38%)<br>4 |
| Polyneuropathy                                                                                                                    |                     |                      |                      |

|                                                  |                     |                        |                      |
|--------------------------------------------------|---------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 10 / 33 (30.30%)<br>10 | 5 / 26 (19.23%)<br>5 |
| Blood and lymphatic system disorders             |                     |                        |                      |
| Anaemia                                          |                     |                        |                      |
| subjects affected / exposed                      | 2 / 16 (12.50%)     | 1 / 33 (3.03%)         | 2 / 26 (7.69%)       |
| occurrences (all)                                | 2                   | 1                      | 2                    |
| Granulocytopenia                                 |                     |                        |                      |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 0 / 33 (0.00%)         | 1 / 26 (3.85%)       |
| occurrences (all)                                | 0                   | 0                      | 1                    |
| Leukopenia                                       |                     |                        |                      |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 33 (3.03%)         | 1 / 26 (3.85%)       |
| occurrences (all)                                | 0                   | 1                      | 1                    |
| Neutropenia                                      |                     |                        |                      |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 3 / 33 (9.09%)         | 2 / 26 (7.69%)       |
| occurrences (all)                                | 0                   | 3                      | 2                    |
| Thrombocytopenia                                 |                     |                        |                      |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 33 (3.03%)         | 0 / 26 (0.00%)       |
| occurrences (all)                                | 0                   | 1                      | 0                    |
| Ear and labyrinth disorders                      |                     |                        |                      |
| Vertigo                                          |                     |                        |                      |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 33 (0.00%)         | 0 / 26 (0.00%)       |
| occurrences (all)                                | 1                   | 0                      | 0                    |
| Eye disorders                                    |                     |                        |                      |
| Intraocular haematoma                            |                     |                        |                      |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 0 / 33 (0.00%)         | 1 / 26 (3.85%)       |
| occurrences (all)                                | 0                   | 0                      | 1                    |
| Lacrimation increased                            |                     |                        |                      |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 33 (0.00%)         | 0 / 26 (0.00%)       |
| occurrences (all)                                | 1                   | 0                      | 0                    |
| Gastrointestinal disorders                       |                     |                        |                      |
| Abdominal pain                                   |                     |                        |                      |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 2 / 33 (6.06%)         | 3 / 26 (11.54%)      |
| occurrences (all)                                | 1                   | 2                      | 3                    |
| Abdominal pain upper                             |                     |                        |                      |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 2 / 33 (6.06%)         | 2 / 26 (7.69%)       |
| occurrences (all)                                | 1                   | 2                      | 2                    |
| chapped lips                                     |                     |                        |                      |

|                             |                 |                  |                 |
|-----------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 0               | 0                | 1               |
| Cheilitis                   |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 0               | 0                | 1               |
| Constipation                |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 9 / 33 (27.27%)  | 6 / 26 (23.08%) |
| occurrences (all)           | 0               | 9                | 6               |
| Diarrhoea                   |                 |                  |                 |
| subjects affected / exposed | 8 / 16 (50.00%) | 17 / 33 (51.52%) | 6 / 26 (23.08%) |
| occurrences (all)           | 11              | 24               | 7               |
| Dyspepsia                   |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 33 (3.03%)   | 3 / 26 (11.54%) |
| occurrences (all)           | 0               | 1                | 3               |
| Dysphagia                   |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 0               | 0                | 1               |
| Eructation                  |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 0               | 0                | 1               |
| Nausea                      |                 |                  |                 |
| subjects affected / exposed | 7 / 16 (43.75%) | 21 / 33 (63.64%) | 9 / 26 (34.62%) |
| occurrences (all)           | 9               | 29               | 10              |
| Oesophagitis                |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 33 (0.00%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 0               | 0                | 1               |
| Stomatitis                  |                 |                  |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 5 / 33 (15.15%)  | 2 / 26 (7.69%)  |
| occurrences (all)           | 1               | 5                | 2               |
| Vomiting                    |                 |                  |                 |
| subjects affected / exposed | 5 / 16 (31.25%) | 12 / 33 (36.36%) | 7 / 26 (26.92%) |
| occurrences (all)           | 6               | 16               | 7               |
| Abdominal distension        |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 33 (3.03%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0               |
| Abdominal rigidity          |                 |                  |                 |

|                                        |                |                |                 |
|----------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Colitis                                |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Dry mouth                              |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Flatulence                             |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Gastritis                              |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Glossodynia                            |                |                |                 |
| subjects affected / exposed            | 1 / 16 (6.25%) | 0 / 33 (0.00%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Haematochezia                          |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Hepatobiliary disorders                |                |                |                 |
| Hepatic pain                           |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 33 (3.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Skin and subcutaneous tissue disorders |                |                |                 |
| Alopecia                               |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 5 / 26 (19.23%) |
| occurrences (all)                      | 0              | 0              | 5               |
| Dermatitis acneiform                   |                |                |                 |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 33 (0.00%) | 3 / 26 (11.54%) |
| occurrences (all)                      | 0              | 0              | 3               |
| Dry skin                               |                |                |                 |
| subjects affected / exposed            | 1 / 16 (6.25%) | 0 / 33 (0.00%) | 2 / 26 (7.69%)  |
| occurrences (all)                      | 1              | 0              | 2               |
| Night sweats                           |                |                |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 33 (6.06%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0              | 2               | 0               |
| Palmar-plantar erythrodysaesthesia syndrome     |                |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 33 (0.00%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 1              | 0               | 0               |
| Papule                                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Pruritus                                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 2 / 26 (7.69%)  |
| occurrences (all)                               | 0              | 1               | 2               |
| Rash                                            |                |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 5 / 33 (15.15%) | 3 / 26 (11.54%) |
| occurrences (all)                               | 1              | 5               | 4               |
| Urticaria                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Renal and urinary disorders                     |                |                 |                 |
| Renal failure                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Postrenal failure                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 33 (0.00%)  | 1 / 26 (3.85%)  |
| occurrences (all)                               | 0              | 0               | 1               |
| Endocrine disorders                             |                |                 |                 |
| Hypothyroidism                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Musculoskeletal and connective tissue disorders |                |                 |                 |
| Arthralgia                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Back pain                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 33 (6.06%)  | 1 / 26 (3.85%)  |
| occurrences (all)                               | 0              | 2               | 1               |
| Muscle spasms                                   |                |                 |                 |

|                               |                |                 |                |
|-------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%) |
| occurrences (all)             | 0              | 1               | 0              |
| Muscular weakness             |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 33 (0.00%)  | 0 / 26 (0.00%) |
| occurrences (all)             | 1              | 0               | 0              |
| Myalgia                       |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 33 (0.00%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 1              | 0               | 1              |
| Neck pain                     |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 33 (0.00%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 0              | 0               | 1              |
| Infections and infestations   |                |                 |                |
| Candida infection             |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 33 (0.00%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 0              | 0               | 1              |
| Clostridium difficile colitis |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 0 / 26 (0.00%) |
| occurrences (all)             | 0              | 1               | 0              |
| Cystitis                      |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 2 / 33 (6.06%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 0              | 2               | 1              |
| Erysipelas                    |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 33 (0.00%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 0              | 0               | 1              |
| Fungal infection              |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 2 / 33 (6.06%)  | 0 / 26 (0.00%) |
| occurrences (all)             | 0              | 2               | 0              |
| Infection                     |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 33 (3.03%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 0              | 1               | 1              |
| Influenza                     |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 33 (0.00%)  | 1 / 26 (3.85%) |
| occurrences (all)             | 0              | 0               | 1              |
| Nasopharyngitis               |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 4 / 33 (12.12%) | 0 / 26 (0.00%) |
| occurrences (all)             | 0              | 4               | 0              |

|                                                                                |                      |                        |                      |
|--------------------------------------------------------------------------------|----------------------|------------------------|----------------------|
| Oesophageal candidiasis<br>subjects affected / exposed<br>occurrences (all)    | 0 / 16 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2    | 0 / 26 (0.00%)<br>0  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                | 0 / 16 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2    | 1 / 26 (3.85%)<br>1  |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 16 (0.00%)<br>0  | 1 / 33 (3.03%)<br>1    | 0 / 26 (0.00%)<br>0  |
| Purulence<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 16 (0.00%)<br>0  | 1 / 33 (3.03%)<br>1    | 0 / 26 (0.00%)<br>0  |
| Rash pustular<br>subjects affected / exposed<br>occurrences (all)              | 0 / 16 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)    | 0 / 16 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2    | 1 / 26 (3.85%)<br>2  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0    | 3 / 26 (11.54%)<br>3 |
| Metabolism and nutrition disorders                                             |                      |                        |                      |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)         | 3 / 16 (18.75%)<br>4 | 11 / 33 (33.33%)<br>11 | 6 / 26 (23.08%)<br>6 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                | 0 / 16 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2    | 0 / 26 (0.00%)<br>0  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 16 (0.00%)<br>0  | 4 / 33 (12.12%)<br>6   | 3 / 26 (11.54%)<br>3 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 05 November 2012 | <p>Changes to better reflect patient populations in clinical routine and corrective changes:</p> <ol style="list-style-type: none"><li>1) Inclusion criteria 10 and 12 were changed into: Patients show a sufficient hepatic and renal function to undergo 5-FU or 5-FU combination treatment, based on the investigators' discretion and in accordance to the recommendation outlined in the SmPCs.</li><li>2) New inclusion criteria: Patients being naïve to 5-FU treatment or having received a maximum of only one treatment cycle of 5-FU without experiencing any AEs/SAEs related to the study drug.</li><li>3) The AUC limits were corrected in the tables of sections 1.4.2 and 5.1.2.</li><li>4) Wording of Primary objective was amended to take into account the changed inclusion criteria: To determine whether pharmacokinetically-guided dose adjustment of 5-FU provides a stable inpatient dose level of 20-30 mg.h /l. The primary analysis will be the comparison of the proportion of patients with AUC within 20 to 30 mg.h/L after the first 5-FU application within the study versus the fourth application within the study.</li><li>5) The use of Leucovorin in the dosage 400mg/m<sup>2</sup> was allowed.</li><li>6) In case no 5-FU plasma concentration has been measured or no valid result has been obtained by the 5-FU measurement, the 5-FU dose in the subsequent cycle will be adapted only according to toxicity.</li><li>7) To make better use of the collected patient data and specimens, an additional purpose of use by the university of Bonn was specified.</li></ol> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27256667>