



## Clinical trial results:

### An exploratory study to investigate the optimal scheduling of chemotherapy in patients with operable colorectal liver metastases

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-003052-40 |
| Trial protocol           | GB             |
| Global end of trial date | 31 July 2015   |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 06 March 2024 |
| First version publication date | 06 March 2024 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | RHMCAN0763 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN32401805 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University Hospital Southampton NHS Foundation Trust   |
| Sponsor organisation address | Southampton General Hospital, Level E, Laboratory & Pathology Block, SCBR, MP 138, Southampton, United Kingdom, SO16 6YD         |
| Public contact               | University of Southampton Clinical Trials Unit, University of Southampton Clinical Trials Unit, 0044 2381205154, ctu@soton.ac.uk |
| Scientific contact           | University of Southampton Clinical Trials Unit, University of Southampton Clinical Trials Unit, 0044 2381205154, ctu@soton.ac.uk |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 01 May 2013  |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 01 May 2013  |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 31 July 2015 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

Currently some patients with colorectal cancer that has spread to the liver can be treated surgically and a significant number will effectively be cured. A prior study has shown that chemotherapy improves the survival of these patients if it is given both before and after the liver surgery. However this causes an increase in the complications of surgery. In this trial we are trying to find out if giving all the chemotherapy after surgery is possible, hence potentially avoiding this problem of complications. If this approach is feasible a larger trial will be undertaken to see if this approach is equivalent in terms of the long term survival of these patients.

Protection of trial subjects:

Eligible participants for the trials were aged 18 years or older, with metastatic resectable liver-limited colorectal cancer, and were recruited from approved study sites. Resectability was confirmed by a liver surgeon and the protocols mandated this as completely removable disease with a microscopic margin of >1 mm achievable and an estimated preoperative margin of  $\geq 5$  mm. The number of tumors was not restricted. All studies were performed in accordance with the Declaration of Helsinki. Institutional or central ethics and research governance approval was obtained, and patients provided written informed consent.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Worldwide total number of subjects   | 20                 |
| EEA total number of subjects         | 20                 |

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)      | 20 |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Eligible participants for the trials were aged 18 years or older, with metastatic resectable liver-limited colorectal cancer, and were recruited from approved study sites. Resectability was confirmed by a liver surgeon and the protocols mandated this as completely removable disease with a microscopic margin of >1 mm achievable

### Pre-assignment

Screening details:

Participants were randomized to receive three months of preoperative and three months of postoperative treatment or six months of postoperative treatment with FOLFOX6 (5-fluorouracil plus oxaliplatin) every two weeks, FOLFIRI (5-fluorouracil plus irinotecan) every two weeks, or CAPOX every three weeks

### Period 1

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

### Arms

|                              |                            |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes                        |
| <b>Arm title</b>             | Surgery, than chemotherapy |

Arm description:

Surgery, than 24weeks standard chemotherapy

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

Dosage and administration details:

24 weeks

|  |   |
|--|---|
| Investigational medicinal product name | CAPOX   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for infusion |
| Routes of administration               | Infusion  |

Dosage and administration details:

24 weeks

|  |   |
|--|---|
| Investigational medicinal product name | mFOLFIRI  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for infusion |
| Routes of administration               | Infusion  |

Dosage and administration details:

24 weeks

|                  |  |
|------------------|--|
| <b>Arm title</b> | 12weeks chemo, surgery, 12 weeks chemo |
|------------------|--|

Arm description:

12 weeks (peri-operative) standard chemotherapy, surgery, 12 weeks (post-operative) standard chemotherapy

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |   |
|--|---|
| Investigational medicinal product name     | mFOLFOX   |
| Investigational medicinal product code     |   |
| Other name                                 |   |
| Pharmaceutical forms                       | Concentrate and solvent for solution for infusion |
| Routes of administration                   | Infusion  |
| Dosage and administration details:         |   |
| 24 weeks (12 weeks pre and post operative) |   |
| Investigational medicinal product name     | CAPOX   |
| Investigational medicinal product code     |   |
| Other name                                 |   |
| Pharmaceutical forms                       | Concentrate and solvent for solution for infusion |
| Routes of administration                   | Infusion  |
| Dosage and administration details:         |   |
| 24 weeks (12 weeks pre and post operative) |   |

| Number of subjects in period 1           | Surgery, than chemotherapy | 12weeks chemo, surgery, 12 weeks chemo |
|--|----------------------------|--|
|  |                            |  |
| Started                                  | 10                         | 10                                     |
| Completed                                | 7                          | 3                                      |
| Not completed                            | 3                          | 7                                      |
| didn't complete the chemotherapy         | 2                          | -                                      |
| progress before surgery                  | -                          | 3                                      |
| no surgical information                  | -                          | 1                                      |
| early termination by Sponsor, no surgery | -                          | 1                                      |
| not completing the postop chemotherapy   | -                          | 2                                      |
| incorrect randomisation                  | 1                          | -                                      |

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Surgery, than chemotherapy             |
| Reporting group description:<br>Surgery, than 24weeks standard chemotherapy   |  |
| Reporting group title   | 12weeks chemo, surgery, 12 weeks chemo |
| Reporting group description:<br>12 weeks (peri-operative) standard chemotherapy, surgery, 12 weeks (post-operative) standard chemotherapy |  |

| Reporting group values                | Surgery, than chemotherapy | 12weeks chemo, surgery, 12 weeks chemo | Total |
|---------------------------------------|----------------------------|--|-------|
| Number of subjects                    | 10                         | 10                                     | 20    |
| Age categorical<br>Units: Subjects    |                            |  |       |
| Age 18-69                             | 9                          | 10                                     | 19    |
| Unknown                               | 1                          | 0                                      | 1     |
| Age continuous<br>Units: years        |                            |  |       |
| median                                | 65                         | 64                                     |       |
| inter-quartile range (Q1-Q3)          | 61 to 69                   | 58 to 66                               | -     |
| Gender categorical<br>Units: Subjects |                            |  |       |
| Female                                | 5                          | 2                                      | 7     |
| Male                                  | 4                          | 8                                      | 12    |
| Unknown                               | 1                          | 0                                      | 1     |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Surgery, than chemotherapy             |
| Reporting group description:<br>Surgery, than 24weeks standard chemotherapy   |  |
| Reporting group title   | 12weeks chemo, surgery, 12 weeks chemo |
| Reporting group description:<br>12 weeks (peri-operative) standard chemotherapy, surgery, 12 weeks (post-operative) standard chemotherapy |  |

### Primary: Recruitment feasibility

|                                   |  |
|-----------------------------------|--|
| End point title                   | Recruitment feasibility <sup>[1]</sup> |
| End point description:            |  |
| End point type                    | Primary                                |
| End point timeframe:<br>32 months |  |

Notes:

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

Justification: No sufficient number for statistical analyses, early termination of the trial.

| End point values                            | Surgery, than chemotherapy | 12weeks chemo, surgery, 12 weeks chemo |  |  |
|---|----------------------------|--|--|--|
| Subject group type                          | Reporting group            | Reporting group                        |  |  |
| Number of subjects analysed                 | 10 <sup>[2]</sup>          | 10 <sup>[3]</sup>                      |  |  |
| Units: Number of patient finished the trial | 7                          | 3                                      |  |  |

Notes:

[2] - Recruited patients

[3] - Recruited patients

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of chemotherapy cycles

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| End point title                   | Proportion of chemotherapy cycles |
| End point description:            |                                   |
| End point type                    | Secondary                         |
| End point timeframe:<br>32 months |                                   |

| End point values            | Surgery, than chemotherapy | 12weeks chemo, surgery, 12 weeks chemo |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            | Reporting group                        |  |  |
| Number of subjects analysed | 9 <sup>[4]</sup>           | 10                                     |  |  |
| Units: Cycles               | 12                         | 6                                      |  |  |

Notes:

[4] - 1 person withdrawn because of wrong randomisation

## Statistical analyses

No statistical analyses for this end point

## Secondary: Surgical mortality and complications

|                                  |                                      |
|----------------------------------|--------------------------------------|
| End point title                  | Surgical mortality and complications |
| End point description:           |                                      |
| End point type                   | Secondary                            |
| End point timeframe:             |                                      |
| within 30 days after the surgery |                                      |

| End point values                             | Surgery, than chemotherapy | 12weeks chemo, surgery, 12 weeks chemo |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            | Reporting group                        |  |  |
| Number of subjects analysed                  | 9 <sup>[5]</sup>           | 5 <sup>[6]</sup>                       |  |  |
| Units: number of patients with complications | 2                          | 4                                      |  |  |

Notes:

[5] - number of patient went through surgery

[6] - number of patient went through surgery

## Statistical analyses

No statistical analyses for this end point

## Secondary: Treatment related toxicity

|                        |                            |
|------------------------|----------------------------|
| End point title        | Treatment related toxicity |
| End point description: |                            |
| End point type         | Secondary                  |
| End point timeframe:   |                            |
| 32 months              |                            |



|   |                            |  |  |  |
|---|----------------------------|--|--|--|
| <b>End point values</b>                       | Surgery, than chemotherapy | 12weeks chemo, surgery, 12 weeks chemo |  |  |
| Subject group type                            | Reporting group            | Reporting group                        |  |  |
| Number of subjects analysed                   | 9 <sup>[7]</sup>           | 10                                     |  |  |
| Units: patients had treatment related adverse | 8                          | 10                                     |  |  |

Notes:

[7] - 1 person withdrawn because of wrong randomisation

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description: -

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description: -

| Serious adverse events                               | Arm A                                       | Arm B           |  |
|--|---|-----------------|--|
| Total subjects affected by serious adverse events    |   |                 |  |
| subjects affected / exposed                          | 3 / 9 (33.33%)                              | 2 / 10 (20.00%) |  |
| number of deaths (all causes)                        | 1   | 2               |  |
| number of deaths resulting from adverse events       | 0   | 0               |  |
| General disorders and administration site conditions |   |                 |  |
| Fever  | Additional description: Fever               |                 |  |
| subjects affected / exposed                          | 1 / 9 (11.11%)                              | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 2                                       | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0                                       | 0 / 0           |  |
| Pain   | Additional description: Pain                |                 |  |
| subjects affected / exposed                          | 1 / 9 (11.11%)                              | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all      | 1 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0                                       | 0 / 0           |  |
| Gastrointestinal disorders                           |   |                 |  |
| Obstruction gastric                                  | Additional description: Obstruction gastric |                 |  |
| subjects affected / exposed                          | 1 / 9 (11.11%)                              | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0                                       | 0 / 0           |  |
| Abdominal pain                                       | Additional description: Abdominal pain      |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 9 (11.11%)                           | 1 / 10 (10.00%) |  |
| occurrences causally related to treatment / all | 1 / 1                                    | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0           |  |
| Hepatobiliary disorders                         |  |                 |  |
| Hepatic pain                                    | Additional description: Hepatic pain     |                 |  |
| subjects affected / exposed                     | 1 / 9 (11.11%)                           | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1                                    | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |  |                 |  |
| Productive cough                                | Additional description: Productive cough |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)                            | 1 / 10 (10.00%) |  |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Arm A   | Arm B             |  |
|---|---|-------------------|--|
| Total subjects affected by non-serious adverse events |   |                   |  |
| subjects affected / exposed                           | 8 / 9 (88.89%)                                  | 10 / 10 (100.00%) |  |
| Vascular disorders                                    |   |                   |  |
| Thromboembolic event                                  | Additional description: Thromboembolic event    |                   |  |
| subjects affected / exposed                           | 1 / 9 (11.11%)                                  | 1 / 10 (10.00%)   |  |
| occurrences (all)                                     | 2   | 1                 |  |
| Hematoma  | Additional description: Hematoma                |                   |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)                                   | 1 / 10 (10.00%)   |  |
| occurrences (all)                                     | 0   | 1                 |  |
| Flushing  | Additional description: Flushing                |                   |  |
| subjects affected / exposed                           | 2 / 9 (22.22%)                                  | 0 / 10 (0.00%)    |  |
| occurrences (all)                                     | 2   | 0                 |  |
| General disorders and administration site conditions  |   |                   |  |
| Injection site reaction                               | Additional description: Injection site reaction |                   |  |
| subjects affected / exposed                           | 1 / 9 (11.11%)                                  | 0 / 10 (0.00%)    |  |
| occurrences (all)                                     | 1   | 0                 |  |
| Edema limbs   | Additional description: Edema limbs             |                   |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 1               |  |
| Fever   | Additional description: Fever                         |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 1               |  |
| Fatigue   | Additional description: Fatigue                       |                 |  |
| subjects affected / exposed                     | 6 / 9 (66.67%)  | 4 / 10 (40.00%) |  |
| occurrences (all)                               | 19  | 9               |  |
| Pain  | Additional description: Pain                          |                 |  |
| subjects affected / exposed                     | 4 / 9 (44.44%)  | 7 / 10 (70.00%) |  |
| occurrences (all)                               | 6   | 11              |  |
| Respiratory, thoracic and mediastinal disorders |   |                 |  |
| Pneumothorax                                    | Additional description: Pneumothorax                  |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 1               |  |
| Laryngopharyngeal dysesthesia                   | Additional description: Laryngopharyngeal dysesthesia |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 1               |  |
| Cough   | Additional description: Cough                         |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 1               |  |
| Epistaxis                                       | Additional description: Epistaxis                     |                 |  |
| subjects affected / exposed                     | 3 / 9 (33.33%)  | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 4   | 1               |  |
| Sore throat                                     | Additional description: Sore throat                   |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 2               |  |
| Dyspnea   | Additional description: Dyspnea                       |                 |  |
| subjects affected / exposed                     | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |  |
| occurrences (all)                               | 1   | 0               |  |
| Productive cough                                | Additional description: Productive cough              |                 |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                               | 0   | 1               |  |
| Psychiatric disorders                           |   |                 |  |

|  |  |                 |  |
|--|--|-----------------|--|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                | Additional description: Anxiety                                |                 |  |
|  | 0 / 9 (0.00%)  | 1 / 10 (10.00%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Depression                             |                 |  |
|  | 1 / 9 (11.11%)   | 1 / 10 (10.00%) |  |
|  | 2  | 1               |  |
|  |  |                 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                               | Additional description: Insomnia                               |                 |  |
|  | 1 / 9 (11.11%)   | 0 / 10 (0.00%)  |  |
|  | 1  | 0               |  |
|  |  |                 |  |
| Psychiatric disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all) | Additional description: Psychiatric disorders - Other, specify |                 |  |
|  | 0 / 9 (0.00%)  | 2 / 10 (20.00%) |  |
|  | 0  | 2               |  |
|  |  |                 |  |
| Investigations   |  |                 |  |
|  | Additional description: Neutrophil count decreased             |                 |  |
|  | 5 / 9 (55.56%)   | 3 / 10 (30.00%) |  |
|  | 8  | 3               |  |
|  |  |                 |  |
|  | Additional description: Weight loss                            |                 |  |
|  | 0 / 9 (0.00%)  | 2 / 10 (20.00%) |  |
|  | 0  | 2               |  |
|  |  |                 |  |
|  | Additional description: Platelet count decreased               |                 |  |
|  | 4 / 9 (44.44%)   | 5 / 10 (50.00%) |  |
|  | 5  | 6               |  |
|  |  |                 |  |
|  | Additional description: Hemoglobin increased                   |                 |  |
|  | 0 / 9 (0.00%)  | 1 / 10 (10.00%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
|  | Additional description: Blood bilirubin increased              |                 |  |
|  | 0 / 9 (0.00%)  | 1 / 10 (10.00%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
|  | Additional description: White blood cell decreased             |                 |  |
|  | 3 / 9 (33.33%)   | 3 / 10 (30.00%) |  |
|  | 3  | 4               |  |
|  |  |                 |  |
|  | Additional description: Alanine aminotransferase increased     |                 |  |
|  | 1 / 9 (11.11%)   | 0 / 10 (0.00%)  |  |
|  | 1  | 0               |  |
|  |  |                 |  |
| Injury, poisoning and procedural complications   |  |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Fall<br>subjects affected / exposed<br>occurrences (all)                                      | Additional description: Fall                                      |                 |  |
|   | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |  |
|   | 1   | 0               |  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)                        | Additional description: Wound complication                        |                 |  |
|   | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
|   | 0   | 1               |  |
| Cardiac disorders   |   |                 |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: Palpitations                              |                 |  |
|   | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |  |
|   | 1   | 0               |  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Atrial fibrillation                       |                 |  |
|   | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
|   | 0   | 1               |  |
| Nervous system disorders  |   |                 |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Peripheral sensory neuropathy             |                 |  |
|   | 1 / 9 (11.11%)  | 1 / 10 (10.00%) |  |
|   | 1   | 4               |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                 | Additional description: Dysgeusia                                 |                 |  |
|   | 4 / 9 (44.44%)  | 4 / 10 (40.00%) |  |
|   | 4   | 7               |  |
| Nervous system disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all) | Additional description: Nervous system disorders - Other, specify |                 |  |
|   | 7 / 9 (77.78%)  | 9 / 10 (90.00%) |  |
|   | 22  | 20              |  |
| Paresthesia<br>subjects affected / exposed<br>occurrences (all)                               | Additional description: Paresthesia                               |                 |  |
|   | 0 / 9 (0.00%)   | 2 / 10 (20.00%) |  |
|   | 0   | 2               |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                  | Additional description: Headache                                  |                 |  |
|   | 0 / 9 (0.00%)   | 2 / 10 (20.00%) |  |
|   | 0   | 2               |  |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)                                 | Additional description: Neuralgia                                 |                 |  |
|   | 2 / 9 (22.22%)  | 4 / 10 (40.00%) |  |
|   | 2   | 4               |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)                                  | Additional description: Lethargy                                  |                 |  |
|   | 1 / 9 (11.11%)  | 5 / 10 (50.00%) |  |
|   | 1   | 7               |  |
| Dysesthesia   | Additional description: Dysesthesia                               |                 |  |
|   |   |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                           | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |  |
| occurrences (all)                                     | 1   | 0               |  |
| Dizziness   | Additional description: Dizziness   |                 |  |
| subjects affected / exposed                           | 2 / 9 (22.22%)  | 0 / 10 (0.00%)  |  |
| occurrences (all)                                     | 2   | 0               |  |
| Blood and lymphatic system disorders                  |   |                 |  |
| Blood and lymphatic system disorders - Other, specify | Additional description: Blood and lymphatic system disorders - Other, specify |                 |  |
| subjects affected / exposed                           | 1 / 9 (11.11%)  | 1 / 10 (10.00%) |  |
| occurrences (all)                                     | 1   | 1               |  |
| Anemia  | Additional description: Anemia  |                 |  |
| subjects affected / exposed                           | 7 / 9 (77.78%)  | 5 / 10 (50.00%) |  |
| occurrences (all)                                     | 8   | 6               |  |
| Febrile neutropenia                                   | Additional description: Febrile neutropenia                                   |                 |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                     | 0   | 1               |  |
| Ear and labyrinth disorders                           |   |                 |  |
| Middle ear inflammation                               | Additional description: Middle ear inflammation                               |                 |  |
| subjects affected / exposed                           | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |  |
| occurrences (all)                                     | 1   | 0               |  |
| Tinnitus  | Additional description: Tinnitus  |                 |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                     | 0   | 1               |  |
| Ear pain  | Additional description: Ear pain  |                 |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                     | 0   | 3               |  |
| Eye disorders   |   |                 |  |
| Eye disorders - Other, specify                        | Additional description: Eye disorders - Other, specify                        |                 |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                     | 0   | 1               |  |
| Watering eyes   | Additional description: Watering eyes   |                 |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                     | 0   | 1               |  |
| Gastrointestinal disorders                            |   |                 |  |
| Nausea  | Additional description: Nausea  |                 |  |
| subjects affected / exposed                           | 6 / 9 (66.67%)  | 7 / 10 (70.00%) |  |
| occurrences (all)                                     | 21  | 12              |  |

|   |   |                 |
|---|---|-----------------|
| Dyspepsia                                   | Additional description: Dyspepsia                                   |                 |
| subjects affected / exposed                 | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |
| occurrences (all)                           | 1   | 0               |
| Vomiting                                    | Additional description: Vomiting                                    |                 |
| subjects affected / exposed                 | 4 / 9 (44.44%)  | 1 / 10 (10.00%) |
| occurrences (all)                           | 5   | 1               |
| Abdominal pain                              | Additional description: Abdominal pain                              |                 |
| subjects affected / exposed                 | 1 / 9 (11.11%)  | 2 / 10 (20.00%) |
| occurrences (all)                           | 1   | 4               |
| Gastrointestinal disorders - Other, specify | Additional description: Gastrointestinal disorders - Other, specify |                 |
| subjects affected / exposed                 | 3 / 9 (33.33%)  | 1 / 10 (10.00%) |
| occurrences (all)                           | 4   | 1               |
| Flatulence                                  | Additional description: Flatulence                                  |                 |
| subjects affected / exposed                 | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |
| occurrences (all)                           | 1   | 0               |
| Dry mouth                                   | Additional description: Dry mouth                                   |                 |
| subjects affected / exposed                 | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |
| occurrences (all)                           | 2   | 0               |
| Abdominal distension                        | Additional description: Abdominal distension                        |                 |
| subjects affected / exposed                 | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |
| occurrences (all)                           | 1   | 0               |
| Diarrhea                                    | Additional description: Diarrhea                                    |                 |
| subjects affected / exposed                 | 7 / 9 (77.78%)  | 7 / 10 (70.00%) |
| occurrences (all)                           | 18  | 12              |
| Constipation                                | Additional description: Constipation                                |                 |
| subjects affected / exposed                 | 4 / 9 (44.44%)  | 4 / 10 (40.00%) |
| occurrences (all)                           | 6   | 6               |
| Small intestinal obstruction                | Additional description: Small intestinal obstruction                |                 |
| subjects affected / exposed                 | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |
| occurrences (all)                           | 0   | 1               |
| Anal pain                                   | Additional description: Anal pain                                   |                 |
| subjects affected / exposed                 | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |
| occurrences (all)                           | 0   | 1               |
| Hemorrhoids                                 | Additional description: Hemorrhoids                                 |                 |



|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                             | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                       | 0   | 1               |  |
| Mucositis oral  | Additional description: Mucositis oral  |                 |  |
| subjects affected / exposed                             | 4 / 9 (44.44%)  | 2 / 10 (20.00%) |  |
| occurrences (all)                                       | 8   | 6               |  |
| Skin and subcutaneous tissue disorders                  |   |                 |  |
| Dry skin  | Additional description: Dry skin  |                 |  |
| subjects affected / exposed                             | 1 / 9 (11.11%)  | 1 / 10 (10.00%) |  |
| occurrences (all)                                       | 1   | 1               |  |
| Skin and subcutaneous tissue disorders - Other, specify | Additional description: Skin and subcutaneous tissue disorders - Other, specify |                 |  |
| subjects affected / exposed                             | 0 / 9 (0.00%)   | 4 / 10 (40.00%) |  |
| occurrences (all)                                       | 0   | 4               |  |
| Alopecia  | Additional description: Alopecia  |                 |  |
| subjects affected / exposed                             | 2 / 9 (22.22%)  | 4 / 10 (40.00%) |  |
| occurrences (all)                                       | 2   | 4               |  |
| Rash maculo-papular                                     | Additional description: Rash maculo-papular                                     |                 |  |
| subjects affected / exposed                             | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                       | 0   | 1               |  |
| Palmar-plantar erythrodysesthesia syndrome              | Additional description: Palmar-plantar erythrodysesthesia syndrome              |                 |  |
| subjects affected / exposed                             | 2 / 9 (22.22%)  | 3 / 10 (30.00%) |  |
| occurrences (all)                                       | 2   | 5               |  |
| Pruritus  | Additional description: Pruritus  |                 |  |
| subjects affected / exposed                             | 1 / 9 (11.11%)  | 0 / 10 (0.00%)  |  |
| occurrences (all)                                       | 1   | 0               |  |
| Purpura   | Additional description: Purpura   |                 |  |
| subjects affected / exposed                             | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                       | 0   | 1               |  |
| Musculoskeletal and connective tissue disorders         |   |                 |  |
| Pain in extremity                                       | Additional description: Pain in extremity                                       |                 |  |
| subjects affected / exposed                             | 1 / 9 (11.11%)  | 1 / 10 (10.00%) |  |
| occurrences (all)                                       | 1   | 4               |  |
| Myalgia   | Additional description: Myalgia   |                 |  |
| subjects affected / exposed                             | 0 / 9 (0.00%)   | 1 / 10 (10.00%) |  |
| occurrences (all)                                       | 0   | 1               |  |
| Back pain   | Additional description: Back pain   |                 |  |

|  |  |                      |  |
|--|--|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1  | 1 / 10 (10.00%)<br>1 |  |
| Arthralgia                                       | Additional description: Arthralgia                                   |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1 |  |
| Arthritis  | Additional description: Arthritis                                    |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1 |  |
| Infections and infestations                      |  |                      |  |
| Mucosal infection                                | Additional description: Mucosal infection                            |                      |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 9 (22.22%)<br>4  | 1 / 10 (10.00%)<br>1 |  |
| Upper respiratory infection                      | Additional description: Upper respiratory infection                  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1 |  |
| Wound infection                                  | Additional description: Wound infection                              |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   | 1 / 10 (10.00%)<br>2 |  |
| Tooth infection                                  | Additional description: Tooth infection                              |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1 |  |
| Infections and infestations - Other, specify     | Additional description: Infections and infestations - Other, specify |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>2  | 4 / 10 (40.00%)<br>4 |  |
| Stoma site infection                             | Additional description: Stoma site infection                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 9 (33.33%)<br>4  | 3 / 10 (30.00%)<br>3 |  |
| Metabolism and nutrition disorders               |  |                      |  |
| Anorexia   | Additional description: Anorexia                                     |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1  | 6 / 10 (60.00%)<br>9 |  |
| Hypokalemia                                      | Additional description: Hypokalemia                                  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1 |  |
| Hyponatremia                                     | Additional description: Hyponatremia                                 |                      |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported