



## Clinical trial results:

### A SINGLE-ARM, MULTICENTER, PHASE II STUDY OF PANITUMUMAB IN COMBINATION WITH CAPECITABINE / OXALIPLATIN IN FIRST-LINE, WILD-TYPE K-RAS METASTATIC COLORECTAL CANCER PATIENTS

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-012655-26 |
| Trial protocol           | GR             |
| Global end of trial date | 26 August 2014 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 14 November 2018 |
| First version publication date | 14 November 2018 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | HE 6A/09 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01215539 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Hellenic Cooperative Oncology Group  |
| Sponsor organisation address | Hatzikonstandi 18, Athens, Greece, 11524   |
| Public contact               | Hellenic Cooperative Oncology Group, Hellenic Cooperative Oncology Group, hecogoff@otenet.gr |
| Scientific contact           | Hellenic Cooperative Oncology Group, Hellenic Cooperative Oncology Group, hecogoff@otenet.gr |

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                       | 26 August 2014 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 26 August 2014 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To estimate the objective response rate in wild-type k-ras, metastatic colorectal cancer patients treated with panitumumab in combination with capecitabine/oxaliplatin as first-line therapy.

Protection of trial subjects:

This study was conducted in conformance with ICH GCP, all applicable laws and regulations. All participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 13 October 2010 |
| 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 | Greece: 78 |
| Worldwide total number of subjects   | 78         |
| EEA total number of subjects         | 78         |

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)                      | 37 |
| From 65 to 84 years                       | 41 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled in the study from 13 October 2010 until 10 September 2013 from 12 sites in Greece.

### Pre-assignment

Screening details:

All potentially eligible subjects underwent screening in order to confirm that all eligibility criteria were met prior to the first administration of the study treatment.

### Period 1

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

### Arms

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Panitumumab+capecitabine+oxaliplatin |
|------------------|--------------------------------------|

Arm description:

Panitumumab was administered by IV infusion on day 1 of each 3-week cycle prior to the administration of chemotherapy. The starting panitumumab dose was 9 mg/kg. Oxaliplatin 130 mg/m<sup>2</sup> IV infusion over 2 hours on Day 1 of each cycle after the administration of panitumumab, capecitabine 2000 mg/m<sup>2</sup> divided in two doses, orally, on Days 1 - 14.

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

Dosage and administration details:

The starting panitumumab dose was 9 mg/kg iv administration on day 1 of each 3-week cycle.

| <b>Number of subjects in period 1</b> | Panitumumab+capecitabine+oxaliplatin |
|---------------------------------------|--------------------------------------|
| Started                               | 78                                   |
| Completed                             | 45                                   |
| Not completed                         | 33                                   |
| Physician decision                    | 5                                    |
| Consent withdrawn by subject          | 6                                    |
| Adverse event, non-fatal              | 3                                    |
| Death                                 | 4                                    |
| Other                                 | 3                                    |
| Progression                           | 10                                   |
| Moved to other hospital               | 2                                    |



## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values | Overall trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 78            | 78    |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Adults (18-64 years)   | 37            | 37    |  |
| From 65-84 years       | 41            | 41    |  |
| 85 years and over      | 0             | 0     |  |
| Age continuous         |               |       |  |
| Units: years           |               |       |  |
| arithmetic mean        | 63.4          |       |  |
| full range (min-max)   | 30.1 to 80.9  | -     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 33            | 33    |  |
| Male                   | 45            | 45    |  |

## End points

### End points reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Panitumumab+capecitabine+oxaliplatin |
|-----------------------|--------------------------------------|

Reporting group description:

Panitumumab was administered by IV infusion on day 1 of each 3-week cycle prior to the administration of chemotherapy. The starting panitumumab dose was 9 mg/kg. Oxaliplatin 130 mg/m<sup>2</sup> IV infusion over 2 hours on Day 1 of each cycle after the administration of panitumumab, capecitabine 2000 mg/m<sup>2</sup> divided in two doses, orally, on Days 1 - 14.

### Primary: Objective Response Rate

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate <sup>[1]</sup> |
|-----------------|--|

End point description:

Response was centrally assessed using RECIST criteria. An objective response was defined as either a complete or a partial response.

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

End point timeframe:

Tumor response was assessed every 6 weeks through week 18 and every 3 months thereafter, until disease progression

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: The percentage of patients that achieved a complete or partial response out of the total number of enrolled patients is provided. No comparisons were performed since this was a single-arm study.

| End point values              | Panitumumab+capecitabine+oxaliplatin |  |  |  |
|-------------------------------|--------------------------------------|--|--|--|
| Subject group type            | Reporting group                      |  |  |  |
| Number of subjects analysed   | 78                                   |  |  |  |
| Units: percentage of patients |                                      |  |  |  |
| number (not applicable)       | 44.9                                 |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression-Free Survival |
|-----------------|---------------------------|

End point description:

Progression-free survival was defined as the time from the date of enrollment to the date of documented disease progression, death or last contact. Deaths without a documented progression were treated as events at the time of death for the PFS analysis.

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

End point timeframe:

Tumor response was assessed every 6 weeks through week 18 and every 3 months thereafter, until disease progression.

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Panitumumab+<br>capecitabine+o<br>xaliplatin |  |  |  |
| Subject group type               | Reporting group                              |  |  |  |
| Number of subjects analysed      | 78   |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 8.1 (6.5 to 9.9)                             |  |  |  |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Kaplan-meier with respect to PFS/PFS_HE6A09.png |
|-----------------------------------|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety profile

|                 |                |
|-----------------|----------------|
| End point title | Safety profile |
|-----------------|----------------|

End point description:

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

End point timeframe:

Adverse Events of all participants were recorded and assessed upon signature of the Informed Consent Form, until 30 days after the last administration of study treatment.

|                              |  |  |  |  |
|------------------------------|--|--|--|--|
| <b>End point values</b>      | Panitumumab+<br>capecitabine+o<br>xaliplatin |  |  |  |
| Subject group type           | Reporting group                              |  |  |  |
| Number of subjects analysed  | 78   |  |  |  |
| Units: number of patients    |  |  |  |  |
| Any adverse event            | 76   |  |  |  |
| Adverse event grade $\geq$ 3 | 54   |  |  |  |
| Adverse event grade $\geq$ 4 | 12   |  |  |  |
| Fatal adverse events         | 6  |  |  |  |
| Serious adverse events       | 27   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

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End point description:

Overall survival was defined as the time from enrollment to the date of death or last contact. Alive patients were censored at the date of their last contact.

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

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End point timeframe:

The median follow-up time was 12.8 months (range 0-39).

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|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Panitumumab+<br>capecitabine+o<br>xaliplatin |  |  |  |
| Subject group type               | Reporting group                              |  |  |  |
| Number of subjects analysed      | 78   |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 23.2 (18.0 to<br>28.8)                       |  |  |  |

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|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Kaplan-meier curve with respect to OS/OS_HE6A09.png |
|-----------------------------------|---|

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### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events of all participants were recorded and assessed upon signature of the Informed Consent Form, until 30 days after the last administration of study treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Panitumumab+capecitabine+oxaliplatin |
|-----------------------|--------------------------------------|

Reporting group description:

Panitumumab was administered by IV infusion on day 1 of each 3-week cycle prior to the administration of chemotherapy. The starting panitumumab dose was 9 mg/kg. Oxaliplatin 130 mg/m<sup>2</sup> IV infusion over 2 hours on Day 1 of each cycle after the administration of panitumumab, capecitabine 2000 mg/m<sup>2</sup> divided in two doses, orally, on Days 1 - 14.

| Serious adverse events                            | Panitumumab+capecitabine+oxaliplatin |  |  |
|---|--------------------------------------|--|--|
| Total subjects affected by serious adverse events |                                      |  |  |
| subjects affected / exposed                       | 27 / 78 (34.62%)                     |  |  |
| number of deaths (all causes)                     | 26                                   |  |  |
| number of deaths resulting from adverse events    | 6                                    |  |  |
| Investigations                                    |                                      |  |  |
| Hyperbilirubinaemia                               |                                      |  |  |
| subjects affected / exposed                       | 1 / 78 (1.28%)                       |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                |  |  |
| deaths causally related to treatment / all        | 0 / 0                                |  |  |
| Neutropenia                                       |                                      |  |  |
| subjects affected / exposed                       | 1 / 78 (1.28%)                       |  |  |
| occurrences causally related to treatment / all   | 1 / 1                                |  |  |
| deaths causally related to treatment / all        | 0 / 0                                |  |  |
| Thrombocytopenia                                  |                                      |  |  |
| subjects affected / exposed                       | 2 / 78 (2.56%)                       |  |  |
| occurrences causally related to treatment / all   | 2 / 2                                |  |  |
| deaths causally related to treatment / all        | 0 / 0                                |  |  |
| Vascular disorders                                |                                      |  |  |
| Deep vein thrombosis                              |                                      |  |  |

|   |                                    |  |  |
|---|------------------------------------|--|--|
| subjects affected / exposed                     | 2 / 78 (2.56%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 2                              |  |  |
| deaths causally related to treatment / all      | 1 / 1                              |  |  |
| Phlebitis superficial                           |                                    |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 0 / 0                              |  |  |
| Ischaemic stroke                                |                                    |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 1 / 1                              |  |  |
| Cardiac disorders                               |                                    |  |  |
| Cardiac arrest                                  |                                    |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 1 / 1                              |  |  |
| Nervous system disorders                        |                                    |  |  |
| Depressed level of consciousness                | Additional description: Somnolence |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 1 / 1                              |  |  |
| Neuropathy                                      |                                    |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 0 / 0                              |  |  |
| Neuropathy sensory                              |                                    |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 0 / 0                              |  |  |
| Blood and lymphatic system disorders            |                                    |  |  |
| Anaemia   |                                    |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                     |  |  |
| occurrences causally related to treatment / all | 1 / 1                              |  |  |
| deaths causally related to treatment / all      | 0 / 0                              |  |  |

|  |                                       |  |  |
|--|---------------------------------------|--|--|
| General disorders and administration site conditions |                                       |  |  |
| Catheter site thrombosis                             |                                       |  |  |
| subjects affected / exposed                          | 1 / 78 (1.28%)                        |  |  |
| occurrences causally related to treatment / all      | 0 / 1                                 |  |  |
| deaths causally related to treatment / all           | 0 / 0                                 |  |  |
| Sudden death   | Additional description: Cause unknown |  |  |
| subjects affected / exposed                          | 1 / 78 (1.28%)                        |  |  |
| occurrences causally related to treatment / all      | 1 / 1                                 |  |  |
| deaths causally related to treatment / all           | 1 / 1                                 |  |  |
| Immune system disorders                              |                                       |  |  |
| Allergic reaction                                    |                                       |  |  |
| subjects affected / exposed                          | 1 / 78 (1.28%)                        |  |  |
| occurrences causally related to treatment / all      | 1 / 1                                 |  |  |
| deaths causally related to treatment / all           | 0 / 0                                 |  |  |
| Gastrointestinal disorders                           |                                       |  |  |
| Diarrhoea  |                                       |  |  |
| subjects affected / exposed                          | 6 / 78 (7.69%)                        |  |  |
| occurrences causally related to treatment / all      | 6 / 6                                 |  |  |
| deaths causally related to treatment / all           | 0 / 0                                 |  |  |
| Ileus  |                                       |  |  |
| subjects affected / exposed                          | 1 / 78 (1.28%)                        |  |  |
| occurrences causally related to treatment / all      | 1 / 1                                 |  |  |
| deaths causally related to treatment / all           | 1 / 1                                 |  |  |
| Vomiting   |                                       |  |  |
| subjects affected / exposed                          | 3 / 78 (3.85%)                        |  |  |
| occurrences causally related to treatment / all      | 3 / 3                                 |  |  |
| deaths causally related to treatment / all           | 0 / 0                                 |  |  |
| Abdominal pain                                       |                                       |  |  |
| subjects affected / exposed                          | 3 / 78 (3.85%)                        |  |  |
| occurrences causally related to treatment / all      | 2 / 3                                 |  |  |
| deaths causally related to treatment / all           | 0 / 0                                 |  |  |
| Intestinal perforation                               |                                       |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 1 / 78 (1.28%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Rectal haemorrhage                              |   |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Intestinal obstruction                          |   |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Respiratory, thoracic and mediastinal disorders |   |  |  |
| Pulmonary embolism                              |   |  |  |
| subjects affected / exposed                     | 2 / 78 (2.56%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Dyspnoea  |   |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 1 / 1   |  |  |
| Chronic obstructive pulmonary disease           | Additional description: Exacerbation of Chronic Obstructive Pulmonary Disease |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 1 / 1   |  |  |
| Infections and infestations                     |   |  |  |
| Infection                                       |   |  |  |
| subjects affected / exposed                     | 2 / 78 (2.56%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Lung infection                                  |   |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Infectious colitis                              |                |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diverticulitis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Hypokalaemia                                    |                |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Panitumumab+cape citabine+oxaliplatin |  |  |
|---|---------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                       |  |  |
| subjects affected / exposed                           | 76 / 78 (97.44%)                      |  |  |
| Vascular disorders                                    |                                       |  |  |
| Phlebitis   |                                       |  |  |
| subjects affected / exposed                           | 1 / 78 (1.28%)                        |  |  |
| occurrences (all)                                     | 1                                     |  |  |
| General disorders and administration site conditions  |                                       |  |  |
| Fatigue   |                                       |  |  |
| subjects affected / exposed                           | 26 / 78 (33.33%)                      |  |  |
| occurrences (all)                                     | 36                                    |  |  |
| Insomnia  |                                       |  |  |
| subjects affected / exposed                           | 1 / 78 (1.28%)                        |  |  |
| occurrences (all)                                     | 1                                     |  |  |
| Fever   |                                       |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed                     | 3 / 78 (3.85%)                                   |  |  |
| occurrences (all)                               | 4  |  |  |
| Edema head and neck                             |  |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                                   |  |  |
| occurrences (all)                               | 1  |  |  |
| Edema limbs                                     |  |  |  |
| subjects affected / exposed                     | 4 / 78 (5.13%)                                   |  |  |
| occurrences (all)                               | 4  |  |  |
| Flu like symptoms                               |  |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                                   |  |  |
| occurrences (all)                               | 1  |  |  |
| Pain  |  |  |  |
| subjects affected / exposed                     | 10 / 78 (12.82%)                                 |  |  |
| occurrences (all)                               | 11   |  |  |
| Immune system disorders                         |  |  |  |
| Allergic reaction                               |  |  |  |
| subjects affected / exposed                     | 5 / 78 (6.41%)                                   |  |  |
| occurrences (all)                               | 9  |  |  |
| Immune system disorder                          | Additional description: Allergy-Dermatology-Skin |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                                   |  |  |
| occurrences (all)                               | 1  |  |  |
| Respiratory, thoracic and mediastinal disorders |  |  |  |
| Hemorrhage pulmonary                            |  |  |  |
| subjects affected / exposed                     | 3 / 78 (3.85%)                                   |  |  |
| occurrences (all)                               | 4  |  |  |
| Bronchospasm                                    |  |  |  |
| subjects affected / exposed                     | 1 / 78 (1.28%)                                   |  |  |
| occurrences (all)                               | 1  |  |  |
| Cough   |  |  |  |
| subjects affected / exposed                     | 4 / 78 (5.13%)                                   |  |  |
| occurrences (all)                               | 4  |  |  |
| Dyspnoea  |  |  |  |
| subjects affected / exposed                     | 4 / 78 (5.13%)                                   |  |  |
| occurrences (all)                               | 5  |  |  |
| Voice alteration                                |  |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 78 (1.28%)<br>1    |  |  |
| Psychiatric disorders<br>Confusional state<br>subjects affected / exposed<br>occurrences (all)         | 1 / 78 (1.28%)<br>1    |  |  |
| Personality change<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 78 (1.28%)<br>1    |  |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 8 / 78 (10.26%)<br>8   |  |  |
| International normalised ratio<br>increased<br>subjects affected / exposed<br>occurrences (all)        | 1 / 78 (1.28%)<br>1    |  |  |
| Activated partial thromboplastin time<br>prolonged<br>subjects affected / exposed<br>occurrences (all) | 1 / 78 (1.28%)<br>1    |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                 | 19 / 78 (24.36%)<br>33 |  |  |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all)            | 36 / 78 (46.15%)<br>67 |  |  |
| Alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                     | 29 / 78 (37.18%)<br>38 |  |  |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 78 (2.56%)<br>3    |  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                          | 20 / 78 (25.64%)<br>31 |  |  |
| Hypercholesterolaemia  |                        |  |  |

|                                     |                  |  |  |
|-------------------------------------|------------------|--|--|
| subjects affected / exposed         | 4 / 78 (5.13%)   |  |  |
| occurrences (all)                   | 4                |  |  |
| Creatinine increased                |                  |  |  |
| subjects affected / exposed         | 2 / 78 (2.56%)   |  |  |
| occurrences (all)                   | 2                |  |  |
| Gamma-glutamyltransferase increased |                  |  |  |
| subjects affected / exposed         | 28 / 78 (35.90%) |  |  |
| occurrences (all)                   | 33               |  |  |
| Hyperkalaemia                       |                  |  |  |
| subjects affected / exposed         | 7 / 78 (8.97%)   |  |  |
| occurrences (all)                   | 8                |  |  |
| Hypermagnesaemia                    |                  |  |  |
| subjects affected / exposed         | 9 / 78 (11.54%)  |  |  |
| occurrences (all)                   | 11               |  |  |
| Hypernatraemia                      |                  |  |  |
| subjects affected / exposed         | 1 / 78 (1.28%)   |  |  |
| occurrences (all)                   | 1                |  |  |
| Hypertriglyceridaemia               |                  |  |  |
| subjects affected / exposed         | 2 / 78 (2.56%)   |  |  |
| occurrences (all)                   | 2                |  |  |
| Hyperuricaemia                      |                  |  |  |
| subjects affected / exposed         | 3 / 78 (3.85%)   |  |  |
| occurrences (all)                   | 4                |  |  |
| Hypoalbuminaemia                    |                  |  |  |
| subjects affected / exposed         | 24 / 78 (30.77%) |  |  |
| occurrences (all)                   | 29               |  |  |
| Hypocalcaemia                       |                  |  |  |
| subjects affected / exposed         | 12 / 78 (15.38%) |  |  |
| occurrences (all)                   | 14               |  |  |
| Hypokalaemia                        |                  |  |  |
| subjects affected / exposed         | 22 / 78 (28.21%) |  |  |
| occurrences (all)                   | 37               |  |  |
| Hypomagnesaemia                     |                  |  |  |
| subjects affected / exposed         | 24 / 78 (30.77%) |  |  |
| occurrences (all)                   | 33               |  |  |



|  |                        |  |  |
|--|------------------------|--|--|
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)  | 10 / 78 (12.82%)<br>15 |  |  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)  | 4 / 78 (5.13%)<br>6    |  |  |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 20 / 78 (25.64%)<br>35 |  |  |
| Blood urea increased<br>subjects affected / exposed<br>occurrences (all)   | 2 / 78 (2.56%)<br>2    |  |  |
| Injury, poisoning and procedural complications<br>Vascular access complication<br>subjects affected / exposed<br>occurrences (all) | 1 / 78 (1.28%)<br>1    |  |  |
| Cardiac disorders<br>Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 1 / 78 (1.28%)<br>1    |  |  |
| Nervous system disorders<br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)  | 5 / 78 (6.41%)<br>6    |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 2 / 78 (2.56%)<br>2    |  |  |
| Mood altered<br>subjects affected / exposed<br>occurrences (all)   | 2 / 78 (2.56%)<br>2    |  |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 1 / 78 (1.28%)<br>1    |  |  |
| Peripheral motor neuropathy<br>subjects affected / exposed<br>occurrences (all)  | 2 / 78 (2.56%)<br>2    |  |  |

|   |  |  |  |
|---|--|--|--|
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                                 | 35 / 78 (44.87%)<br>53                                 |  |  |
| Neuropathy cranial<br>alternative dictionary used: CTCAE<br>3<br>subjects affected / exposed<br>occurrences (all) | 3 / 78 (3.85%)<br>4                                    |  |  |
| Speech disorder<br>subjects affected / exposed<br>occurrences (all)   | 1 / 78 (1.28%)<br>1                                    |  |  |
| Blood and lymphatic system disorders  |  |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)   | 28 / 78 (35.90%)<br>45                                 |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)  | 26 / 78 (33.33%)<br>46                                 |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)   | 24 / 78 (30.77%)<br>44                                 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)  | 26 / 78 (33.33%)<br>51                                 |  |  |
| Ear and labyrinth disorders   |  |  |  |
| Ear and labyrinth disorder- other   | Additional description: Partial temporary hearing loss |  |  |
| subjects affected / exposed<br>occurrences (all)  | 1 / 78 (1.28%)<br>1                                    |  |  |
| Eye disorders   |  |  |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)   | 1 / 78 (1.28%)<br>1                                    |  |  |
| Ocular surface disease<br>subjects affected / exposed<br>occurrences (all)  | 4 / 78 (5.13%)<br>4                                    |  |  |
| Gastrointestinal disorders  |  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Constipation                |                  |  |  |
| subjects affected / exposed | 11 / 78 (14.10%) |  |  |
| occurrences (all)           | 13               |  |  |
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 34 / 78 (43.59%) |  |  |
| occurrences (all)           | 60               |  |  |
| Flatulence                  |                  |  |  |
| subjects affected / exposed | 1 / 78 (1.28%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Dry mouth                   |                  |  |  |
| subjects affected / exposed | 2 / 78 (2.56%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Dysphagia                   |                  |  |  |
| subjects affected / exposed | 4 / 78 (5.13%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Stomatitis                  |                  |  |  |
| subjects affected / exposed | 10 / 78 (12.82%) |  |  |
| occurrences (all)           | 13               |  |  |
| Nausea                      |                  |  |  |
| subjects affected / exposed | 17 / 78 (21.79%) |  |  |
| occurrences (all)           | 26               |  |  |
| Vomiting                    |                  |  |  |
| subjects affected / exposed | 16 / 78 (20.51%) |  |  |
| occurrences (all)           | 26               |  |  |
| Gastrointestinal pain       |                  |  |  |
| subjects affected / exposed | 1 / 78 (1.28%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Abdominal distension        |                  |  |  |
| subjects affected / exposed | 1 / 78 (1.28%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Esophagitis                 |                  |  |  |
| subjects affected / exposed | 1 / 78 (1.28%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Hemorrhage gastrointestinal |                  |  |  |
| subjects affected / exposed | 1 / 78 (1.28%)   |  |  |
| occurrences (all)           | 1                |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| Skin and subcutaneous tissue disorders     |                  |  |  |
| Acne                                       |                  |  |  |
| subjects affected / exposed                | 13 / 78 (16.67%) |  |  |
| occurrences (all)                          | 13               |  |  |
| Cheilitis                                  |                  |  |  |
| subjects affected / exposed                | 1 / 78 (1.28%)   |  |  |
| occurrences (all)                          | 1                |  |  |
| Skin disorder                              |                  |  |  |
| subjects affected / exposed                | 6 / 78 (7.69%)   |  |  |
| occurrences (all)                          | 6                |  |  |
| Dry skin                                   |                  |  |  |
| subjects affected / exposed                | 6 / 78 (7.69%)   |  |  |
| occurrences (all)                          | 6                |  |  |
| Palmar-plantar erythrodysesthesia syndrome |                  |  |  |
| subjects affected / exposed                | 20 / 78 (25.64%) |  |  |
| occurrences (all)                          | 23               |  |  |
| Nail disorder                              |                  |  |  |
| subjects affected / exposed                | 4 / 78 (5.13%)   |  |  |
| occurrences (all)                          | 4                |  |  |
| Photosensitivity reaction                  |                  |  |  |
| subjects affected / exposed                | 1 / 78 (1.28%)   |  |  |
| occurrences (all)                          | 1                |  |  |
| Pruritus                                   |                  |  |  |
| subjects affected / exposed                | 4 / 78 (5.13%)   |  |  |
| occurrences (all)                          | 4                |  |  |
| Rash                                       |                  |  |  |
| subjects affected / exposed                | 56 / 78 (71.79%) |  |  |
| occurrences (all)                          | 63               |  |  |
| Hyperhidrosis                              |                  |  |  |
| subjects affected / exposed                | 1 / 78 (1.28%)   |  |  |
| occurrences (all)                          | 1                |  |  |
| Hair growth rate abnormal                  |                  |  |  |
| subjects affected / exposed                | 2 / 78 (2.56%)   |  |  |
| occurrences (all)                          | 2                |  |  |
| Subcutaneous abscess                       |                  |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 78 (1.28%)<br>1   |  |  |
| Renal and urinary disorders<br>Hematuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Hemorrhage GU<br>alternative dictionary used: CTCAE<br>3<br>subjects affected / exposed<br>occurrences (all)  | 1 / 78 (1.28%)<br>1<br><br><br>1 / 78 (1.28%)<br>1  |  |  |
| Infections and infestations<br>Infections and infestations- Other<br>specify<br>subjects affected / exposed<br>occurrences (all)<br><br>Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Viral infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Diverticulitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nail infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Herpes virus infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 78 (5.13%)<br>5<br><br>1 / 78 (1.28%)<br>1<br><br>1 / 78 (1.28%)<br>1<br><br>1 / 78 (1.28%)<br>1<br><br>1 / 78 (1.28%)<br>1<br><br>1 / 78 (1.28%)<br>1<br><br>1 / 78 (1.28%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all)  | 19 / 78 (24.36%)<br>24  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Hyperglycemia               |                  |  |  |
| subjects affected / exposed | 32 / 78 (41.03%) |  |  |
| occurrences (all)           | 65               |  |  |
| Hypoglycaemia               |                  |  |  |
| subjects affected / exposed | 1 / 78 (1.28%)   |  |  |
| occurrences (all)           | 1                |  |  |

## **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