# Clinical trial results:
# A Phase II, Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of RO5520985 (Vanucizumab) Plus FOLFOX Versus Bevacizumab Plus FOLFOX in Patients With Previously Untreated Metastatic Colorectal Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2013-005108-32 |
| Trial protocol | BE AT ES IT GB |
| Global end of trial date | 01 February 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 29 July 2017 |
| First version publication date | 29 July 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | BP29262 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02141295 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche Ltd |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, 4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 29 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 February 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of Study BP29262 is to estimate the efficacy of RO5520985 in combination with oxaliplatin, folinic acid, and 5 fluorouracil (mFOLFOX-6) vs. bevacizumab in combination with mFOLFOX-6, as measured by progression-free survival (PFS).

Protection of trial subjects:

This study was fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Conference on Harmonization (ICH) Tripartite Guideline (January 1997) or with local law.

Background therapy:

mFOLFOX
Both arms received mFOLFOX as background therapy.
In the induction therapy, participants received oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Evidence for comparator:

Bevacizumab

| | |
|---|---|
| Actual start date of recruitment | 30 June 2014 |
| 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 | Spain: 105 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | United States: 59 |
| Country: Number of subjects enrolled | Australia: 5 |
| Worldwide total number of subjects | 189 |
| EEA total number of subjects | 125 |

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) | 101 |
| From 65 to 84 years | 88 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants with previously untreated metastatic colorectal cancer (mCRC) as defined by RECIST v1.1 were enrolled globally from 7 countries.

### Period 1

| | |
|---|---|
| Period 1 title | Overall study (part 2) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Vanucizumab + mFOLFOX-6 |

Arm description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Vanucizumab |
| Investigational medicinal product code | |
| Other name | RO5520985 |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

2000 mg as IV infusion

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

Dosage and administration details:

85 mg/m^2 as IV infusion

| | |
|---|---|
| Investigational medicinal product name | 5-FU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion

| | |
|---|---|
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

400 mg/m^2 as IV infusion

| | |
|---|---|
| **Arm title** | Bevacizumab + mFOLFOX-6 |

Arm description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

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

Dosage and administration details:

5 milligram per kilogram (mg/kg) as IV infusion

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

Dosage and administration details:

85 mg/m^2 as IV infusion

| | |
|---|---|
| Investigational medicinal product name | 5-FU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion

| | |
|---|---|
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

400 mg/m^2 as IV infusion

| **Number of subjects in period 1** | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 |
|---|---|---|
| Started | 94 | 95 |
| Completed | 17 | 21 |
| Not completed | 77 | 74 |
| Physician decision | 17 | 12 |
| Consent withdrawn by subject | 9 | 4 |
| Adverse event, non-fatal | 16 | 10 |
| TBC | 5 | 9 |
| Non-compliance | 1 | - |
| Study terminated by sponsor | - | 1 |
| Progressive disease | 29 | 38 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Vanucizumab + mFOLFOX-6 |
|---|---|

Reporting group description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| Reporting group title | Bevacizumab + mFOLFOX-6 |
|---|---|

Reporting group description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| Reporting group values | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | Total |
|---|---|---|---|
| Number of subjects | 94 | 95 | 189 |
| Age Categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 48 | 53 | 101 |
| From 65-84 years | 46 | 42 | 88 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 62.7 | 62.3 | |
| standard deviation | ± 11 | ± 10.6 | - |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 38 | 57 | 95 |
| Male | 56 | 38 | 94 |

### Subject analysis sets

| Subject analysis set title | Safety run-in (part 1) |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

8 eligible participants received 2000 milligrams (mg) vanucizumab + mFOLFOX-6 every two weeks for up to 8 cycles in order to confirm the dose and schedule for the overall study.

| Reporting group values | Safety run-in (part 1) | | |
|---|---|---|---|
| Number of subjects | 8 | | |

| | | | |
|---|---|---|---|
| Age Categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 4 | | |
| From 65-84 years | 4 | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 63.3 | | |
| standard deviation | ± 10.8 | | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 3 | | |
| Male | 5 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Vanucizumab + mFOLFOX-6 |

Reporting group description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| | |
|---|---|
| Reporting group title | Bevacizumab + mFOLFOX-6 |

Reporting group description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| | |
|---|---|
| Subject analysis set title | Safety run-in (part 1) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

8 eligible participants received 2000 milligrams (mg) vanucizumab + mFOLFOX-6 every two weeks for up to 8 cycles in order to confirm the dose and schedule for the overall study.

### Primary: Progression-free Survival (PFS), time to event

| | |
|---|---|
| End point title | Progression-free Survival (PFS), time to event |

End point description:

Efficacy of vanucizumab was evaluated in terms of PFS as Investigator-Assessed Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

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

End point timeframe:

Baseline, every 8 weeks, up to approximately 29 months

| End point values | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 95 | | |
| Units: Number of days | | | | |
| median (confidence interval 95%) | 343 (304 to 386) | 333 (263 to 388) | | |

## Statistical analyses

| Statistical analysis title | Stratified analysis (metastatic sites from IVRS) |
|---|---|

Statistical analysis description:

Kaplan-Meier methods were used to estimate median PFS for each treatment arm and the 95% CIs for median PFS were computed using the Brookmeyer and Crowley method.
The stratified Cox proportional hazard was used to estimate the hazard ratio (i.e., the magnitude of the treatment effect) and the corresponding 95% confidence interval. The stratification factors are number of metastatic sites (1 vs. >1) and country/region (USA vs rest of the world).

| | |
|---|---|
| Comparison groups | Bevacizumab + mFOLFOX-6 v Vanucizumab + mFOLFOX-6 |
| Number of subjects included in analysis | 189 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7581 [1] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.44 |

Notes:

[1] - log-rank

## Secondary: Percentage of Participants With Objective Response (ORR) as Assessed Using RECIST v. 1.1

| End point title | Percentage of Participants With Objective Response (ORR) as Assessed Using RECIST v. 1.1 |
|---|---|

End point description:

Efficacy of vanucizumab was evaluated in terms of Percentage of Participants With ORR as Investigator-Assessed Using RECIST v. 1.1. Best Overall Confirmed Response.

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

End point timeframe:

Baseline (within 28 days prior to Day 1), then every 8 weeks until progressive disease (PD), start of other anticancer therapy, withdrawal of consent, or death (up to approximately 29 months)

| End point values | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 95 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Responders, total | 41.5 (31.53 to 51.45) | 45.3 (35.25 to 55.27) | | |
| Complete response (CR) | 0 (0 to 3.85) | 3.2 (0.66 to 8.95) | | |
| Partial response (PR) | 41.5 (31.41 to 52.12) | 42.1 (32.04 to 52.67) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Objective Response, as Assessed Using RECIST v. 1.1

| End point title | Duration of Objective Response, as Assessed Using RECIST v. 1.1 |
|---|---|

End point description:

Efficacy of vanucizumab was evaluated in terms of duration of objective response as assessed using RECIST v. 1.1.
This was computed using the PFS definition with death on study (deaths that occurred outside the 30 days window from the last study treatment are excluded).

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

End point timeframe:

Baseline (within 28 days prior to Day 1), then every 8 weeks until PD, start of other anticancer therapy, withdrawal of consent, or death (up to approximately 29 months)

| End point values | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 95 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 282 (274 to 453) | 315 (220 to 392) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

| End point title | Overall Survival (OS) |
|---|---|

End point description:

Efficacy of vanucizumab was evaluated in terms of OS as the time from randomization until death from any cause.
99999 = data not estimable because there were only few deaths in both treatment arms (immature data).

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

End point timeframe:

Baseline until death from any cause (maximum up to approximately 3.5 years)

| End point values | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 95 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 622 (622 to 99999) | 630 (630 to 99999) | | |

### Statistical analyses

| Statistical analysis title | Stratified analysis (metastatic sites from IVRS) |
|---|---|

Statistical analysis description:

Kaplan-Meier methods were used to estimate median OS for each treatment arm and the 95% CIs for median OS were computed using the Brookmeyer and Crowley method.
The stratified Cox proportional hazard was used to estimate the hazard ratio (i.e., the magnitude of the treatment effect) and the corresponding 95% confidence interval. The stratification factors are number of metastatic sites (1 vs. >1) and country/region (USA vs rest of the world).

| | |
|---|---|
| Comparison groups | Vanucizumab + mFOLFOX-6 v Bevacizumab + mFOLFOX-6 |
| Number of subjects included in analysis | 189 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5626 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 1.6 |

### Secondary: Percentage of Participants With Adverse Events (AEs)

| End point title | Percentage of Participants With Adverse Events (AEs) |
|---|---|

End point description:

Safety is evaluated in terms of percentage of participants with at least one serious adverse event and percentage of participants with at least one adverse event.

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

End point timeframe:

Up to approximately 29 months

| End point values | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | Safety run-in (part 1) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 93 | 95 | 8 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Serious Adverse events | 44.1 | 42.1 | 37.5 | |
| Adverse events | 100 | 100 | 100 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Human Anti-human Antibodies (HAHAs) Against Vanucizumab

| End point title | Number of Participants With Human Anti-human Antibodies (HAHAs) Against Vanucizumab[2] |
|---|---|

End point description:

Safety is evaluated in terms of number of participants with Human Anti-human Antibodies (HAHAs) Against Vanucizumab.

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

End point timeframe:

Pre-dose (0 hours [hrs]) on Day 1 Cycle 1 (D1C1), D1C5, D1C9, D1C13 (cycle length=14 days), end of study (EoS, within 28 to 42 days after last dose, latest at 29 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the immunogenicity of Bevacizumab is already known and well characterized, no immunogenicity was evaluated for Bevacizumab.

| End point values | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 93 | 8 | | |
| Units: Number of Participants | 1 | 2 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Plasma Concentration-Time Curve (AUC) of Vanucizumab

| End point title | Area Under the Plasma Concentration-Time Curve (AUC) of Vanucizumab[3] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of AUC, values are reported for cycle 8 of part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered

Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 45 | 3 | | |
| Units: hr*ug/ml | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 8 | 82100 (± 31.6) | 112000 (± 11.2) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Plasma Concentration (Cmax) of Vanucizumab

| End point title | Maximum Observed Plasma Concentration (Cmax) of Vanucizumab[4] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of Cmax, values are reported for cycle 8 for both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 64 | 6 | | |
| Units: ug/ml | | | | |
| geometric mean (geometric coefficient of variation) | 794 (± 38.2) | 685 (± 17.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Minimum Observed Plasma Concentration (Clast) of Vanucizumab

| End point title | Minimum Observed Plasma Concentration (Clast) of Vanucizumab[5] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of Clast, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs]), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose), at PD/ EoS (latest at 29 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: ug/ml | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 8 | 361 (± 39.8) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Reach Cmax (Tmax) of Vanucizumab

| End point title | Time to Reach Cmax (Tmax) of Vanucizumab[6] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of Tmax for cycles 8 for both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 64 | 6 | | |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Cycle 8 | 1.58 (0.5 to 4.77) | 4.04 (0.5 to 5.25) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Terminal Half-Life (t1/2) of Vanucizumab

| End point title | Plasma Terminal Half-Life (t1/2) of Vanucizumab[7] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of t1/2, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| End point values | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 37 | 3 | | |
| Units: hr | | | | |
| geometric mean (geometric coefficient of variation) | 157 (± 30.3) | 202 (± 12.4) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Clearance at Steady State (CLss) of Vanucizumab

| End point title | Plasma Clearance at Steady State (CLss) of Vanucizumab[8] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of CLss, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 37 | 3 | | |
| Units: ml/hr | | | | |
| geometric mean (geometric coefficient of variation) | 18 (± 29) | 15.3 (± 26.7) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State (Vss) of Vanucizumab

| End point title | Volume of Distribution at Steady State (Vss) of Vanucizumab[9] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of Vss, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 37 | 3 | | |
| Units: ml | | | | |
| geometric mean (geometric coefficient of variation) | 4140 (± 29.7) | 4400 (± 25.1) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax Accumulation Ratio (AR) of Vanucizumab

| End point title | Cmax Accumulation Ratio (AR) of Vanucizumab[10] |
|---|---|

End point description:

PK profile of vanucizumab was evaluated in terms of Cmax Ratio, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

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

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

| **End point values** | Vanucizumab + mFOLFOX-6 | Safety run-in (part 1) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 64 | 5 | | |
| Units: N/A | | | | |
| geometric mean (geometric coefficient of variation) | 1.63 (± 36.2) | 1.51 (± 27.2) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 28 days after the last dose of study drug (maximum treatment time = approximately 29 months).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Vanucizumab + mFOLFOX-6 |

Reporting group description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| | |
|---|---|
| Reporting group title | Bevacizumab + mFOLFOX-6 |

Reporting group description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

| | |
|---|---|
| Reporting group title | Safety run-in |

Reporting group description:

8 eligible participants received 2000 milligrams (mg) vanucizumab + mFOLFOX-6 every two weeks for up to 8 cycles in order to confirm the dose and schedule for the overall study.

| Serious adverse events | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | Safety run-in |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 41 / 93 (44.09%) | 40 / 95 (42.11%) | 3 / 8 (37.50%) |
| number of deaths (all causes) | 16 | 21 | 3 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| INFECTED NEOPLASM | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumor obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| AORTIC THROMBOSIS | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VASOSPASM | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COMPLICATION ASSOCIATED WITH DEVICE | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NON−CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 4 / 95 (4.21%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| FEMALE GENITAL TRACT FISTULA | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EPISTAXIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| DEVICE DISLOCATION | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEVICE OCCLUSION | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL ANASTOMOTIC LEAK | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PELVIC FRACTURE | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TOXICITY TO VARIOUS AGENTS | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial Ischaemia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL CORD COMPRESSION | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile Neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 5 / 95 (5.26%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 2 / 95 (2.11%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 3 / 95 (3.16%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal ulcer | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 3 / 95 (3.16%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterovesical fistula | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 93 (3.23%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| BILE DUCT STONE | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| CERVICAL SPINAL STENOSIS | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PATHOLOGICAL FRACTURE | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIARRHOEA INFECTIOUS | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENTEROCOCCAL BACTERAEMIA | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS ACUTE | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Splenic abscess | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 93 (1.08%) | 4 / 95 (4.21%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FAILURE TO THRIVE | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Vanucizumab + mFOLFOX-6 | Bevacizumab + mFOLFOX-6 | Safety run-in |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 90 / 93 (96.77%) | 94 / 95 (98.95%) | 8 / 8 (100.00%) |
| Vascular disorders | | | |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 41 / 93 (44.09%) | 26 / 95 (27.37%) | 5 / 8 (62.50%) |
| occurrences (all) | 65 | 49 | 9 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 6 / 95 (6.32%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 6 | 1 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 40 / 93 (43.01%) | 42 / 95 (44.21%) | 3 / 8 (37.50%) |
| occurrences (all) | 90 | 127 | 6 |
| Chest discomfort | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 3 / 95 (3.16%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 26 / 93 (27.96%) | 21 / 95 (22.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 31 | 25 | 1 |
| Mass | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 21 / 93 (22.58%) | 31 / 95 (32.63%) | 4 / 8 (50.00%) |
| occurrences (all) | 40 | 66 | 6 |
| Oedema peripheral | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 2 / 95 (2.11%) | 3 / 8 (37.50%) |
| occurrences (all) | 11 | 2 | 5 |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 93 (17.20%) | 15 / 95 (15.79%) | 1 / 8 (12.50%) |
| occurrences (all) | 22 | 21 | 1 |
| Temperature intolerance | | | |
| subjects affected / exposed | 11 / 93 (11.83%) | 10 / 95 (10.53%) | 1 / 8 (12.50%) |
| occurrences (all) | 15 | 16 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 9 / 95 (9.47%) | 1 / 8 (12.50%) |
| occurrences (all) | 12 | 12 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 12 / 93 (12.90%) | 9 / 95 (9.47%) | 1 / 8 (12.50%) |
| occurrences (all) | 12 | 12 | 2 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 93 (10.75%) | 10 / 95 (10.53%) | 1 / 8 (12.50%) |
| occurrences (all) | 11 | 12 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 19 / 93 (20.43%) | 28 / 95 (29.47%) | 2 / 8 (25.00%) |
| occurrences (all) | 26 | 36 | 2 |
| Hiccups | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 2 / 95 (2.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 4 | 3 | 1 |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 6 / 95 (6.32%) | 1 / 8 (12.50%) |
| occurrences (all) | 3 | 6 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 5 / 95 (5.26%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 9 / 93 (9.68%) | 8 / 95 (8.42%) | 1 / 8 (12.50%) |
| occurrences (all) | 9 | 8 | 1 |
| Depression | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 1 / 95 (1.05%) | 1 / 8 (12.50%) |
| occurrences (all) | 6 | 1 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 11 / 93 (11.83%) | 12 / 95 (12.63%) | 0 / 8 (0.00%) |
| occurrences (all) | 11 | 13 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 5 / 95 (5.26%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 5 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 7 / 95 (7.37%) | 0 / 8 (0.00%) |
| occurrences (all) | 7 | 7 | 0 |
| GAMMA−GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 4 / 95 (4.21%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 5 | 1 |
| Lipase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 93 (2.15%) | 8 / 95 (8.42%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 8 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 4 / 95 (4.21%) | 0 / 8 (0.00%) |
| occurrences (all) | 25 | 6 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 11 / 93 (11.83%) | 13 / 95 (13.68%) | 0 / 8 (0.00%) |
| occurrences (all) | 12 | 13 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 2 / 95 (2.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 4 | 2 | 1 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 4 | 3 | 2 |
| Infusion related reaction | | | |
| subjects affected / exposed | 19 / 93 (20.43%) | 12 / 95 (12.63%) | 1 / 8 (12.50%) |
| occurrences (all) | 26 | 17 | 1 |
| Nervous system disorders | | | |
| Aphonia | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 12 / 95 (12.63%) | 1 / 8 (12.50%) |
| occurrences (all) | 12 | 17 | 1 |
| Dysaesthesia | | | |
| subjects affected / exposed | 15 / 93 (16.13%) | 22 / 95 (23.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 32 | 79 | 3 |
| Dysgeusia | | | |
| subjects affected / exposed | 16 / 93 (17.20%) | 22 / 95 (23.16%) | 5 / 8 (62.50%) |
| occurrences (all) | 16 | 26 | 6 |
| Headache | | | |
| subjects affected / exposed | 15 / 93 (16.13%) | 18 / 95 (18.95%) | 2 / 8 (25.00%) |
| occurrences (all) | 16 | 29 | 2 |
| Hypoaesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 3 | 2 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 16 / 93 (17.20%) | 26 / 95 (27.37%) | 3 / 8 (37.50%) |
| occurrences (all) | 29 | 62 | 8 |
| Neurotoxicity | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 14 | 2 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 15 / 93 (16.13%) | 17 / 95 (17.89%) | 1 / 8 (12.50%) |
| occurrences (all) | 17 | 24 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 32 / 93 (34.41%) | 27 / 95 (28.42%) | 2 / 8 (25.00%) |
| occurrences (all) | 79 | 70 | 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 12 / 95 (12.63%) | 3 / 8 (37.50%) |
| occurrences (all) | 7 | 19 | 3 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 3 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 39 / 93 (41.94%) | 42 / 95 (44.21%) | 4 / 8 (50.00%) |
| occurrences (all) | 52 | 63 | 6 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 8 / 95 (8.42%) | 3 / 8 (37.50%) |
| occurrences (all) | 6 | 8 | 4 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Lacrimation increase | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 93 (4.30%) | 5 / 95 (5.26%) | 2 / 8 (25.00%) |
| occurrences (all) | 5 | 6 | 2 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 26 / 93 (27.96%) | 18 / 95 (18.95%) | 2 / 8 (25.00%) |
| occurrences (all) | 33 | 19 | 3 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 3 / 95 (3.16%) | 0 / 8 (0.00%) |
| occurrences (all) | 8 | 3 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 12 / 95 (12.63%) | 0 / 8 (0.00%) |
| occurrences (all) | 9 | 12 | 0 |
| Constipation | | | |
| subjects affected / exposed | 24 / 93 (25.81%) | 29 / 95 (30.53%) | 3 / 8 (37.50%) |
| occurrences (all) | 35 | 48 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 54 / 93 (58.06%) | 54 / 95 (56.84%) | 6 / 8 (75.00%) |
| occurrences (all) | 102 | 127 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 5 / 95 (5.26%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 11 / 93 (11.83%) | 8 / 95 (8.42%) | 0 / 8 (0.00%) |
| occurrences (all) | 14 | 12 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 3 | 1 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 51 / 93 (54.84%) | 55 / 95 (57.89%) | 6 / 8 (75.00%) |
| occurrences (all) | 90 | 98 | 6 |
| Odynophagia | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 1 / 95 (1.05%) | 0 / 8 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 4 | 1 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 4 / 95 (4.21%) | 1 / 8 (12.50%) |
| occurrences (all) | 3 | 4 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 15 / 93 (16.13%) | 11 / 95 (11.58%) | 1 / 8 (12.50%) |
| occurrences (all) | 23 | 15 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 29 / 93 (31.18%) | 27 / 95 (28.42%) | 1 / 8 (12.50%) |
| occurrences (all) | 39 | 45 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 14 / 95 (14.74%) | 1 / 8 (12.50%) |
| occurrences (all) | 5 | 14 | 1 |
| Nail disorder | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| PALMAR−PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 15 / 95 (15.79%) | 2 / 8 (25.00%) |
| occurrences (all) | 12 | 21 | 2 |
| Rash | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 8 / 95 (8.42%) | 0 / 8 (0.00%) |
| occurrences (all) | 8 | 10 | 0 |
| Skin hyperpigmentation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 93 (4.30%) | 4 / 95 (4.21%) | 2 / 8 (25.00%) |
| occurrences (all) | 5 | 5 | 2 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 6 / 95 (6.32%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 8 | 0 |
| Proteinuria | | | |
| subjects affected / exposed | 11 / 93 (11.83%) | 9 / 95 (9.47%) | 1 / 8 (12.50%) |
| occurrences (all) | 14 | 15 | 5 |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 8 / 95 (8.42%) | 2 / 8 (25.00%) |
| occurrences (all) | 4 | 10 | 4 |
| Back pain | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 14 / 95 (14.74%) | 1 / 8 (12.50%) |
| occurrences (all) | 9 | 16 | 1 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 5 / 95 (5.26%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 6 | 2 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 9 / 93 (9.68%) | 7 / 95 (7.37%) | 1 / 8 (12.50%) |
| occurrences (all) | 12 | 9 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 7 / 95 (7.37%) | 0 / 8 (0.00%) |
| occurrences (all) | 11 | 10 | 0 |
| Pain in extremitiy | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 6 / 95 (6.32%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 7 | 2 |
| Pain in jaw | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 2 / 95 (2.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 6 | 4 | 0 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Ear infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 95 (1.05%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Furuncle | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingivitis | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 2 / 95 (2.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 4 | 3 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 8 / 95 (8.42%) | 2 / 8 (25.00%) |
| occurrences (all) | 8 | 11 | 2 |
| Oral candidiasis | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 1 / 95 (1.05%) | 1 / 8 (12.50%) |
| occurrences (all) | 5 | 2 | 1 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 3 / 95 (3.16%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 3 | 2 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 1 / 95 (1.05%) | 1 / 8 (12.50%) |
| occurrences (all) | 4 | 1 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 13 / 95 (13.68%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 14 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 10 / 95 (10.53%) | 2 / 8 (25.00%) |
| occurrences (all) | 11 | 13 | 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 28 / 93 (30.11%) | 32 / 95 (33.68%) | 1 / 8 (12.50%) |
| occurrences (all) | 44 | 66 | 3 |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 93 (8.60%) | 7 / 95 (7.37%) | 1 / 8 (12.50%) |
| occurrences (all) | 10 | 7 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 6 / 95 (6.32%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 10 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 95 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 10 / 95 (10.53%) | 0 / 8 (0.00%) |
| occurrences (all) | 9 | 10 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 April 2014 | Amended due to FDA request<br>• An exclusion criterion for metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses of large volume, was added.<br>• An exclusion criterion for history of gross hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to randomization was added.<br>• Further vanucizumab pharmacokinetic (PK) samples were added in Cycle 1 and Cycle 8. |
| 16 May 2014 | Amended due to request following VHP in Europe<br>• For the Part I safety run-in, simultaneous (i.e., same day) treatment administration to several patients, for the first 6 patients, was no longer allowed. Treatment of the first 6 patients was sequential i.e., there was always at least 1 working day between the first vanucizumab administration of one enrolled patient and the first vanucizumab administration of the next enrolled patient. |
| 10 June 2014 | • The revisions in Protocol Version 2 (EU) and Protocol Version 1 (US) were combined into a harmonized Version 3. |
| 08 September 2015 | • The sample size was increased from 140 patients to approximately 190 patients in order to compensate for early patient discontinuations and thereby to ensure that the number of PFS events required for the core analysis (n = 80) would be reached. |
| 10 February 2016 | • Risk mitigation measures were implemented as described in the Dear Investigator Letter (DIL) of 24 December 2015. The reason for submission of the DIL was to inform investigators that 10% of patients across two studies with vanucizumab had experienced gastrointestinal (GI) perforations (including GI fistula and intra abdominal abscess) and to inform them about additional risk mitigation measures that were made effective immediately to ensure the utmost safety and well- being of the patients, including:<br>– Re-consenting ongoing patients to inform them about the increased risk of GI perforation associated with the blinded study drug treatment.<br>– Excluding patients with a history of peptic ulcer disease, diverticulitis, or colitis within 6 months prior to Day 1 of Cycle 1.<br>– Excluding patients with abdominal surgery or interventions within 60 days prior to Day 1 of Cycle 1.<br>– Excluding patients with colonic prosthesis (stent) implant in place.<br>– Permanently discontinuing study drug treatment in patients with confirmed intestinal sub-occlusive syndrome/occlusive syndrome/intestinal obstruction.<br>– Advising patients to immediately contact the study physician in case they experience clinical symptoms suggestive of intestinal sub-/occlusion/intestinal obstruction or GI perforation such as acute, persisting and/or increasing abdominal pain, nausea and vomiting, etc. in order to initiate the appropriate diagnostic and therapeutic measures for this condition.<br>– Prohibiting concomitant chronic use of non steroidal anti inflammatory drugs (NSAIDs) while receiving study drugs. However, for the symptomatic relief of medical conditions (e.g. headache, fever) sporadic or short-term intake of oral NSAIDs was allowed, when co-administered with proton pump inhibitors to reduce potential gastrointestinal damage. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported