# Clinical trial results:
# A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-6624 Combined with FOLFIRI as Second Line Treatment for Metastatic KRAS Mutant Colorectal Adenocarcinoma that has Progressed Following a First Line Oxaliplatin- and Fluoropyrimidine-Containing Regimen

## Summary

| | |
|---|---|
| EudraCT number | 2011-003754-61 |
| Trial protocol | IT ES DE PL |
| Global end of trial date | 27 February 2015 |
| **Results information** | |
| Result version number | v2 (current) |
| This version publication date | 03 April 2019 |
| First version publication date | 15 July 2016 |
| Version creation reason | • Correction of full data set<br>Adding 1 missing SAE and typo to a non-serious AE. |

## Trial information

| **Trial identification** | |
|---|---|
| Sponsor protocol code | GS-US-295-0203 |
| **Additional study identifiers** | |
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01479465 |
| WHO universal trial number (UTN) | - |

Notes:

| **Sponsors** | |
|---|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |

Notes:

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 February 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 February 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

This study was to compare the additive efficacy of simtuzumab (SIM; GS-6624) versus placebo in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) as measured by improvement in progression-free survival (PFS) in adults with metastatic KRAS mutant colorectal adenocarcinoma who have progressed following a first line oxaliplatin- and fluoropyrimidine-containing regimen.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Spain: 30 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | United States: 148 |
| Country: Number of subjects enrolled | Russian Federation: 29 |
| Worldwide total number of subjects | 266 |
| EEA total number of subjects | 89 |

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) | 175 |
| From 65 to 84 years | 90 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Russia, and the European Union (EU). The first participant was screened on 15 December 2011. The last study visit occurred on 27 February 2015.

### Pre-assignment

Screening details:

358 participants were screened.

### Period 1

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

Blinding implementation details:

Note: Part A was open-label and nonrandomized, while Part B was randomized and double-blind.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | SIM (Part A) |

Arm description:

SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Simtuzumab |
| Investigational medicinal product code | |
| Other name | GS-6624 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Simtuzumab 700 mg prepared by reconstituting vials of simtuzumab in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of l-leucovorin (LV) 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus fluorouracil (FU) 400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

| | |
|---|---|
| **Arm title** | SIM 200 mg (Part B) |

Arm description:

SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Simtuzumab |
| Investigational medicinal product code | |
| Other name | GS-6624 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Simtuzumab 200 mg prepared by reconstituting vials of simtuzumab and placebo in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of LV 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU 400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

| | |
|---|---|
| **Arm title** | SIM 700 mg (Part B) |

Arm description:

SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Simtuzumab |
| Investigational medicinal product code | |
| Other name | GS-6624 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Simtuzumab 700 mg prepared by reconstituting vials of simtuzumab in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of LV 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU 400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

| | |
|---|---|
| **Arm title** | Placebo (Part B) |

Arm description:

Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle

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

Dosage and administration details:

Placebo prepared by reconstituting vials of simtuzumab placebo in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of LV 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU

400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

| **Number of subjects in period 1[1]** | SIM (Part A) | SIM 200 mg (Part B) | SIM 700 mg (Part B) |
|---|---|---|---|
| Started | 11 | 85 | 84 |
| Completed Follow-up | 11 | 85 | 84 |
| Completed | 0 | 0 | 0 |
| Not completed | 11 | 85 | 84 |
| Adverse event, serious fatal | - | 2 | 1 |
| Subject Withdrew Consent | - | 2 | 1 |
| Adverse event, non-fatal | - | 4 | 3 |
| Death | - | - | 1 |
| Investigator's Discretion | 1 | 2 | 4 |
| Study Discontinued by Sponsor | - | 5 | 3 |
| Subject Request | 1 | 4 | 2 |
| Lost to follow-up | - | 1 | - |
| Disease Progression | 9 | 65 | 69 |

| **Number of subjects in period 1[1]** | Placebo (Part B) |
|---|---|
| Started | 80 |
| Completed Follow-up | 80 |
| Completed | 0 |
| Not completed | 80 |
| Adverse event, serious fatal | 2 |
| Subject Withdrew Consent | 4 |
| Adverse event, non-fatal | - |
| Death | - |
| Investigator's Discretion | 3 |
| Study Discontinued by Sponsor | 7 |
| Subject Request | 3 |
| Lost to follow-up | - |
| Disease Progression | 61 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 6 participants who were randomized but not treated are not included in the subject disposition table.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | SIM (Part A) |
| Reporting group description: | |
| SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle | |

| | |
|---|---|
| Reporting group title | SIM 200 mg (Part B) |
| Reporting group description: | |
| SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |
| Reporting group title | SIM 700 mg (Part B) |
| Reporting group description: | |
| SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |

| | |
|---|---|
| Reporting group title | Placebo (Part B) |
| Reporting group description: | |
| Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |

| Reporting group values | SIM (Part A) | SIM 200 mg (Part B) | SIM 700 mg (Part B) |
|---|---|---|---|
| Number of subjects | 11 | 85 | 84 |
| Age categorical<br>Units: Subjects | | | |
| ≥ 65 years | 4 | 36 | 28 |
| < 65 years | 7 | 49 | 56 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 57.3 | 62.6 | 60.1 |
| standard deviation | ± 14.09 | ± 11.39 | ± 9.76 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 32 | 48 |
| Male | 5 | 53 | 36 |
| Race<br>Units: Subjects | | | |
| White | 8 | 74 | 71 |
| Black or African American | 2 | 5 | 7 |
| Asian | 1 | 5 | 1 |
| Native Hawaiian or Pacific Islander | 0 | 0 | 1 |
| Not Permitted | 0 | 1 | 3 |
| Missing | 0 | 0 | 1 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 3 | 7 | 8 |
| Not Hispanic or Latino | 8 | 75 | 73 |
| Not Permitted | 0 | 3 | 3 |

| Reporting group values | Placebo (Part B) | Total | |
|---|---|---|---|
| Number of subjects | 80 | 260 | |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |
| ≥ 65 years | 23 | 91 | |
| < 65 years | 57 | 169 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58.8 | | |
| standard deviation | ± 11.78 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 41 | 127 | |
| Male | 39 | 133 | |
| Race<br>Units: Subjects | | | |
| White | 67 | 220 | |
| Black or African American | 8 | 22 | |
| Asian | 1 | 8 | |
| Native Hawaiian or Pacific Islander | 1 | 2 | |
| Not Permitted | 3 | 7 | |
| Missing | 0 | 1 | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 5 | 23 | |
| Not Hispanic or Latino | 70 | 226 | |
| Not Permitted | 5 | 11 | |

## End points

### End points reporting groups

| Reporting group title | SIM (Part A) |
|---|---|
| Reporting group description: | |
| SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle | |

| Reporting group title | SIM 200 mg (Part B) |
|---|---|
| Reporting group description: | |
| SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |

| Reporting group title | SIM 700 mg (Part B) |
|---|---|
| Reporting group description: | |
| SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |

| Reporting group title | Placebo (Part B) |
|---|---|
| Reporting group description: | |
| Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |

### Primary: Progression-Free Survival

| End point title | Progression-Free Survival |
|---|---|
| End point description: | |
| Progression-free survival (PFS) was defined as the time from the date of randomization to the earliest event time of a) death regardless of cause, or b) first indication of disease progression. PFS was analyzed using Kaplan-Meier (KM) estimates.<br><br>Participants in the Full Analysis Set (participants who were randomized and received at least 1 dose of study drug) with available data were analyzed. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 27 months | |

| End point values | SIM (Part A) | SIM 200 mg (Part B) | SIM 700 mg (Part B) | Placebo (Part B) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 85 | 84 | 80 |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.7 (1.8 to 10) | 5.4 (3.4 to 5.6) | 5.5 (4 to 7.1) | 5.8 (4.9 to 9) |

### Statistical analyses

| Statistical analysis title | PFS - SIM 200 mg vs Placebo |
|---|---|
| Statistical analysis description: | |
| The difference in PFS among the treatment groups was assessed using Kaplan-Meier methods and the stratified log-rank test, adjusted for the stratification factors. | |
| Comparison groups | Placebo (Part B) v SIM 200 mg (Part B) |

| | |
|---|---|
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0395 [1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 2.06 |

Notes:

[1] - P-value was based on a two-sided log-rank test stratified based on the 2 level Eastern Cooperative Oncology Group (ECOG) performance status (0 or > 0) at randomization.

| **Statistical analysis title** | PFS - SIM 700 mg vs Placebo |
|---|---|

Statistical analysis description:

The difference in PFS among the treatment groups was assessed using Kaplan-Meier methods and the stratified log-rank test, adjusted for the stratification factors.

| | |
|---|---|
| Comparison groups | SIM 700 mg (Part B) v Placebo (Part B) |
| Number of subjects included in analysis | 164 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1042 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.89 |

Notes:

[2] - P-value was based on a two-sided log-rank test stratified based on the 2 level ECOG performance status (0 or > 0) at randomization.

## Secondary: Overall Survival

| End point title | Overall Survival |
|---|---|

End point description:

Overall survivial (OS) was defined as the time from the date of randomization to death regardless of cause. The OS was analyzed using KM estimates.

Participants in the Full Analysis Set with available data were analyzed.

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

End point timeframe:

Up to 33 months

| End point values | SIM (Part A) | SIM 200 mg (Part B) | SIM 700 mg (Part B) | Placebo (Part B) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 85 | 84 | 80 |
| Units: months | | | | |
| median (confidence interval 95%) | 9.8 (3.5 to 22.3) | 10.5 (9.2 to 12.6) | 11.4 (9.7 to 15.6) | 16.3 (12 to 19.5) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Objective Response Rate

| End point title | Objective Response Rate |
|---|---|

End point description:

Objective response was assessed by the RECIST criteria (ver. 1.1) as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD). Objective response rate (ORR) was defined as the proportion of participants who achieved a CR or PR.

Participants in the Full Analysis Set with available data were analyzed.

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

End point timeframe:

Up to 27 months

| End point values | SIM (Part A) | SIM 200 mg (Part B) | SIM 700 mg (Part B) | Placebo (Part B) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 85 | 84 | 80 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 9.1 (0.2 to 41.3) | 5.9 (1.9 to 13.2) | 11.9 (5.9 to 20.8) | 10 (4.4 to 18.8) |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Up to 33 months | |
| Adverse event reporting additional description: | |
| Safety Analysis Set: participants in the Full Analysis Set grouped for analyses with treatment assignments designated according to the actual study drug received. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo (Part B) |
| Reporting group description: | |
| Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |
| Reporting group title | SIM 200 mg (Part B) |
| Reporting group description: | |
| SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |
| Reporting group title | SIM 700 mg (Part B) |
| Reporting group description: | |
| SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle | |
| Reporting group title | SIM (Part A) |
| Reporting group description: | |
| SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle | |

| Serious adverse events | Placebo (Part B) | SIM 200 mg (Part B) | SIM 700 mg (Part B) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 80 (33.75%) | 24 / 85 (28.24%) | 17 / 84 (20.24%) |
| number of deaths (all causes) | 3 | 2 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant ascites | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava occlusion | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 2 / 84 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Death | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |

| | | | |
|---|---|---|---|
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 2 / 85 (2.35%) | 2 / 84 (2.38%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract inflammation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary infarction | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Confusional state | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |

| | | | |
|---|---|---|---|
| Radius fracture | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |

| | | | |
|---|---|---|---|
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 3 / 85 (3.53%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 85 (1.18%) | 2 / 84 (2.38%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 2 / 85 (2.35%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 3 / 85 (3.53%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 2 / 84 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Subileus | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Enteritis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 acute | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |

| **Serious adverse events** | SIM (Part A) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant ascites | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour thrombosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Superior vena cava occlusion | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Venous thrombosis | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General disorders and administration site conditions | | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthenia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune system disorders | | | | |
| Hypersensitivity | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract inflammation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Mental status changes | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachycardia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Presyncope | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| Febrile neutropenia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anaemia | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leukopenia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombocytopenia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorders | | | | |
| Vomiting | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subileus | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anal fistula | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enteritis | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal perforation | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal and urinary disorders | | | | |
| Nephrolithiasis | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal failure acute | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal impairment | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract disorder | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Back pain | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Sepsis | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|---|---|---|---|
| Urosepsis | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteraemia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis viral | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Klebsiella infection | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Dehydration | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypokalaemia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diabetic ketoacidosis | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Electrolyte imbalance | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemia | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyponatraemia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Placebo (Part B) | SIM 200 mg (Part B) | SIM 700 mg (Part B) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 80 (95.00%) | 80 / 85 (94.12%) | 79 / 84 (94.05%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 2 / 85 (2.35%) | 4 / 84 (4.76%) |
| occurrences (all) | 3 | 2 | 5 |
| Flushing | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 2 / 85 (2.35%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Peripheral coldness | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 34 / 80 (42.50%) | 38 / 85 (44.71%) | 43 / 84 (51.19%) |
| occurrences (all) | 47 | 55 | 70 |
| Asthenia | | | |
| subjects affected / exposed | 12 / 80 (15.00%) | 13 / 85 (15.29%) | 12 / 84 (14.29%) |
| occurrences (all) | 22 | 33 | 26 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 10 / 80 (12.50%) | 14 / 85 (16.47%) | 7 / 84 (8.33%) |
| occurrences (all) | 11 | 17 | 18 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 80 (13.75%) | 10 / 85 (11.76%) | 11 / 84 (13.10%) |
| occurrences (all) | 21 | 11 | 17 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 14 / 85 (16.47%) | 10 / 84 (11.90%) |
| occurrences (all) | 4 | 15 | 12 |
| Chest pain | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 85 (1.18%) | 5 / 84 (5.95%) |
| occurrences (all) | 4 | 1 | 5 |
| Malaise | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 85 (1.18%) | 5 / 84 (5.95%) |
| occurrences (all) | 1 | 2 | 5 |
| Catheter site pain | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences (all) | 1 | 0 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences (all) | 1 | 0 | 1 |
| Catheter site rash | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Feeling jittery | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 10 / 80 (12.50%) | 10 / 85 (11.76%) | 14 / 84 (16.67%) |
| occurrences (all) | 10 | 10 | 18 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 80 (12.50%) | 9 / 85 (10.59%) | 11 / 84 (13.10%) |
| occurrences (all) | 11 | 11 | 13 |
| Epistaxis | | | |
| subjects affected / exposed | 10 / 80 (12.50%) | 5 / 85 (5.88%) | 4 / 84 (4.76%) |
| occurrences (all) | 13 | 5 | 4 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 0 / 85 (0.00%) | 8 / 84 (9.52%) |
| occurrences (all) | 4 | 0 | 9 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 85 (2.35%) | 4 / 84 (4.76%) |
| occurrences (all) | 3 | 2 | 4 |
| Hiccups | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences (all) | 1 | 1 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 3 / 85 (3.53%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Throat tightness | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 9 / 80 (11.25%) | 5 / 85 (5.88%) | 8 / 84 (9.52%) |
| occurrences (all) | 10 | 5 | 10 |
| Anxiety | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 5 / 85 (5.88%) | 4 / 84 (4.76%) |
| occurrences (all) | 6 | 5 | 5 |
| Depression | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 3 / 85 (3.53%) | 3 / 84 (3.57%) |
| occurrences (all) | 2 | 4 | 3 |
| Agitation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Anger | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mood swings | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 9 / 85 (10.59%) | 6 / 84 (7.14%) |
| occurrences (all) | 9 | 11 | 6 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 6 / 85 (7.06%) | 4 / 84 (4.76%) |
| occurrences (all) | 5 | 6 | 4 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 4 / 85 (4.71%) | 4 / 84 (4.76%) |
| occurrences (all) | 7 | 4 | 4 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 4 / 85 (4.71%) | 5 / 84 (5.95%) |
| occurrences (all) | 4 | 4 | 6 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 3 / 85 (3.53%) | 3 / 84 (3.57%) |
| occurrences (all) | 6 | 3 | 4 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 85 (2.35%) | 1 / 84 (1.19%) |
| occurrences (all) | 3 | 5 | 1 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 9 / 85 (10.59%) | 13 / 84 (15.48%) |
| occurrences (all) | 9 | 11 | 20 |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 6 / 85 (7.06%) | 8 / 84 (9.52%) |
| occurrences (all) | 6 | 7 | 9 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 7 / 85 (8.24%) | 7 / 84 (8.33%) |
| occurrences (all) | 5 | 7 | 7 |
| Headache | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 3 / 85 (3.53%) | 6 / 84 (7.14%) |
| occurrences (all) | 4 | 4 | 8 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 2 / 85 (2.35%) | 3 / 84 (3.57%) |
| occurrences (all) | 4 | 2 | 3 |
| Parosmia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 35 / 80 (43.75%) | 42 / 85 (49.41%) | 40 / 84 (47.62%) |
| occurrences (all) | 81 | 77 | 91 |
| Anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 19 / 80 (23.75%) | 23 / 85 (27.06%) | 18 / 84 (21.43%) |
| occurrences (all) | 30 | 27 | 34 |
| Leukopenia | | | |
| subjects affected / exposed | 9 / 80 (11.25%) | 13 / 85 (15.29%) | 13 / 84 (15.48%) |
| occurrences (all) | 35 | 24 | 43 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 10 / 85 (11.76%) | 11 / 84 (13.10%) |
| occurrences (all) | 12 | 13 | 16 |
| Eye disorders | | | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 43 / 80 (53.75%) | 36 / 85 (42.35%) | 42 / 84 (50.00%) |
| occurrences (all) | 93 | 58 | 92 |
| Nausea | | | |
| subjects affected / exposed | 37 / 80 (46.25%) | 38 / 85 (44.71%) | 42 / 84 (50.00%) |
| occurrences (all) | 93 | 60 | 100 |
| Vomiting | | | |
| subjects affected / exposed | 25 / 80 (31.25%) | 21 / 85 (24.71%) | 23 / 84 (27.38%) |
| occurrences (all) | 50 | 30 | 37 |
| Abdominal pain | | | |
| subjects affected / exposed | 18 / 80 (22.50%) | 16 / 85 (18.82%) | 22 / 84 (26.19%) |
| occurrences (all) | 31 | 21 | 28 |
| Constipation | | | |
| subjects affected / exposed | 17 / 80 (21.25%) | 18 / 85 (21.18%) | 21 / 84 (25.00%) |
| occurrences (all) | 23 | 23 | 37 |
| Stomatitis | | | |
| subjects affected / exposed | 17 / 80 (21.25%) | 14 / 85 (16.47%) | 9 / 84 (10.71%) |
| occurrences (all) | 58 | 19 | 17 |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 80 (7.50%) | 8 / 85 (9.41%) | 6 / 84 (7.14%) |
| occurrences (all) | 7 | 8 | 6 |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 4 / 85 (4.71%) | 4 / 84 (4.76%) |
| occurrences (all) | 9 | 6 | 4 |
| Dry mouth | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 2 / 85 (2.35%) | 3 / 84 (3.57%) |
| occurrences (all) | 7 | 3 | 3 |
| Abdominal distension | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 2 / 85 (2.35%) | 1 / 84 (1.19%) |
| occurrences (all) | 4 | 2 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 3 / 85 (3.53%) | 1 / 84 (1.19%) |
| occurrences (all) | 3 | 3 | 1 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 0 / 85 (0.00%) | 2 / 84 (2.38%) |
| occurrences (all) | 6 | 0 | 2 |
| Dysphagia | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences (all) | 4 | 0 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 3 / 85 (3.53%) | 1 / 84 (1.19%) |
| occurrences (all) | 2 | 5 | 1 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 85 (2.35%) | 0 / 84 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral mucosal erythema | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Alopecia | | | |
| subjects affected / exposed | 21 / 80 (26.25%) | 20 / 85 (23.53%) | 22 / 84 (26.19%) |
| occurrences (all) | 21 | 20 | 22 |
| Dry skin | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 2 / 85 (2.35%) | 5 / 84 (5.95%) |
| occurrences (all) | 5 | 4 | 6 |
| Rash | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 4 / 85 (4.71%) | 3 / 84 (3.57%) |
| occurrences (all) | 13 | 7 | 3 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 2 / 85 (2.35%) | 3 / 84 (3.57%) |
| occurrences (all) | 3 | 2 | 4 |
| Night sweats | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 1 / 85 (1.18%) | 3 / 84 (3.57%) |
| occurrences (all) | 4 | 1 | 3 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 85 (2.35%) | 2 / 84 (2.38%) |
| occurrences (all) | 1 | 2 | 3 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin wrinkling | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 3 / 85 (3.53%) | 0 / 84 (0.00%) |
| occurrences (all) | 7 | 3 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nocturia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 9 / 85 (10.59%) | 9 / 84 (10.71%) |
| occurrences (all) | 6 | 10 | 11 |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 4 / 85 (4.71%) | 5 / 84 (5.95%) |
| occurrences (all) | 4 | 5 | 5 |
| Muscle spasms | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 0 / 85 (0.00%) | 5 / 84 (5.95%) |
| occurrences (all) | 7 | 0 | 8 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 85 (1.18%) | 6 / 84 (7.14%) |
| occurrences (all) | 5 | 1 | 7 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 85 (1.18%) | 5 / 84 (5.95%) |
| occurrences (all) | 8 | 1 | 5 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 85 (0.00%) | 2 / 84 (2.38%) |
| occurrences (all) | 2 | 0 | 3 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 2 / 85 (2.35%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Muscle atrophy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 5 / 85 (5.88%) | 9 / 84 (10.71%) |
| occurrences (all) | 8 | 7 | 9 |
| Upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 80 (6.25%) | 4 / 85 (4.71%) | 2 / 84 (2.38%) |
| occurrences (all) | 5 | 4 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 85 (2.35%) | 2 / 84 (2.38%) |
| occurrences (all) | 1 | 2 | 2 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 85 (2.35%) | 0 / 84 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 22 / 80 (27.50%) | 14 / 85 (16.47%) | 21 / 84 (25.00%) |
| occurrences (all) | 29 | 17 | 35 |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 80 (10.00%) | 8 / 85 (9.41%) | 10 / 84 (11.90%) |
| occurrences (all) | 11 | 11 | 13 |
| Dehydration | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 5 / 85 (5.88%) | 6 / 84 (7.14%) |
| occurrences (all) | 5 | 6 | 7 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 4 / 85 (4.71%) | 3 / 84 (3.57%) |
| occurrences (all) | 2 | 4 | 5 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 2 / 85 (2.35%) | 3 / 84 (3.57%) |
| occurrences (all) | 8 | 2 | 7 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 85 (2.35%) | 2 / 84 (2.38%) |
| occurrences (all) | 1 | 2 | 2 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 85 (0.00%) | 2 / 84 (2.38%) |
| occurrences (all) | 0 | 0 | 2 |

| **Non-serious adverse events** | SIM (Part A) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Flushing | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Peripheral coldness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 11 (81.82%) | | |
| occurrences (all) | 19 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 5 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Catheter site rash | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Feeling abnormal | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Axillary pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Feeling jittery | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hiccups | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Throat tightness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | | |
| occurrences (all) | 6 | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Anger | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Mood swings | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Weight decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |

| | | | | |
|---|---|---|---|---|
| Dizziness<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | | |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>2 | | | |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 2 / 11 (18.18%)<br>2 | | | |
| Headache<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | | |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>3 | | | |
| Parosmia<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | | |
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | | |
| VIIth nerve paralysis<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | | |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all) | 6 / 11 (54.55%)<br>14 | | | |
| Anaemia<br>subjects affected / exposed<br>occurrences (all) | 3 / 11 (27.27%)<br>4 | | | |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>5 | | | |
| Thrombocytopenia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Eye pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 11 (81.82%) | | |
| occurrences (all) | 15 | | |
| Nausea | | | |
| subjects affected / exposed | 9 / 11 (81.82%) | | |
| occurrences (all) | 17 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | | |
| occurrences (all) | 12 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | | |
| occurrences (all) | 7 | | |
| Constipation | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | | |
| occurrences (all) | 5 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 3 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Dry mouth | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 3 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Oral pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Oral mucosal erythema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | | |
| occurrences (all) | 6 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|---|---|
| Rash | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Swelling face | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Skin disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Skin wrinkling | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Nocturia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Arthralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Muscle atrophy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Muscle tightness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | | |
| occurrences (all) | 7 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 29 September 2011 | The protocol was revised to provide specific guidance on dose modification for study drug and FOLFIRI. |
| 07 November 2011 | The protocol was revised to exclude subjects with metastatic BRAF mutant colorectal adenocarcinoma, to further clarify the dose modification for FOLFIRI, to specify enrolled subjects must have experienced radiographic disease progression following first line therapy, and to clarify that prior irinotecan therapy for metastatic disease was not permitted, but prior adjuvant therapy with irinotecan was allowed. |
| 08 March 2012 | The protocol was revised in response to questions received during the European Voluntary Harmonization Procedure assessment (to specify that the KRAS mutated, histologically confirmed adenocarcinoma of the colon or rectum was not to be amenable to complete surgical resection, to specify that the subject must have received first-line combination therapy containing oxaliplatin and a fluoropyrimidine with or without bevacizumab for metastatic disease, to specify that the subject must not be a candidate for further oxaliplatin, to clarify cardiac conditions and define hypertension parameters that would exclude subjects from the study, to describe emergency unblinding procedures, and to add an interim analysis. |
| 05 September 2012 | The protocol was revised to include analyses for systemic biomarkers related to complete response (CR) pathophysiology or GS-6624 mechanism of action such as circulating LOXL2 and TIMP-1<br>levels and to clarify inclusion/exclusion criteria. |
| 20 March 2014 | The protocol was revised to change the assessment of progressive disease for PFS from Independent Radiology Review to determination by Principal Investigator, to remove the interim analysis, and to indicate that Gilead would assess the continuation of the development of SIM in colorectal cancer if the primary objective of the study was not met and could decide to prematurely discontinue the study. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes: