



Clinical trial results:

Randomized, Double-Blind Phase 2 Study of Axitinib (AG 013736) With or Without Dose

Titration in Patients with Metastatic Renal Cell Carcinoma

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2008-007786-23 |
| Trial protocol | ES CZ DE |
| Global end of trial date | 29 February 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 16 March 2017 |
| First version publication date | 16 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A4061046 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00835978 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 Est 42nd Street, New York, United States, 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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 | 29 February 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to prospectively evaluate the safety and efficacy of axitinib with and without dose titration in patients with metastatic renal cell carcinoma (mRCC)

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki as amended by the 52nd World Medical Association (WMA) General Assembly in October 20001.

Informed consent was obtained from each patient (or patient's legally authorized representative) before the patient was admitted to the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 11 September 2009 |
| 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 | Czech Republic: 18 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Japan: 44 |
| Country: Number of subjects enrolled | Russian Federation: 45 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | United States: 90 |
| Worldwide total number of subjects | 213 |
| EEA total number of subjects | 34 |

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) | 136 |
| From 65 to 84 years | 77 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 49 centers in Czech Republic, Germany, Japan, Russian Federation, Spain, and United States (US).

Pre-assignment

Screening details:

Participants were enrolled in a 4-week lead-in period, during which they received axitinib 5 milligram (mg) twice a day (BID). After the lead-in period, participants meeting randomization criteria were then randomized to one of the two treatment arms. Participants, not meeting criteria, continued study without dose titration (non-randomized arm).

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 | Subject, Investigator |

Blinding implementation details:

The dose titration in the randomized arms (Arm A and B) was double-blinded. The interactive voice response system (IVRS) assigned study treatment on Cycle 2 Day 1. The IVRS maintained the blind.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Active Titration Arm |

Arm description:

Participants initially received axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Axitinib |
| Investigational medicinal product code | AG-013736 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

| | |
|------------------|-----------------------|
| Arm title | Placebo Titration Arm |
|------------------|-----------------------|

Arm description:

Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|--------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

| | |
|------------------|--------------------|
| Arm title | Non-randomized Arm |
|------------------|--------------------|

Arm description:

Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Axitinib |
| Investigational medicinal product code | AG-013736 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants not eligible for randomization received axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

| | |
|------------------|-------------------------------------|
| Arm title | Discontinued Prior to Randomization |
|------------------|-------------------------------------|

Arm description:

Participants who discontinued before they were randomized to any of the treatment or non-randomized arms.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Axitinib |
| Investigational medicinal product code | AG-013736 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants who discontinued before they were randomized to any of the treatment or non-randomized arms.

| Number of subjects in period 1 | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm |
|---------------------------------------|----------------------|-----------------------|--------------------|
| Started | 56 | 56 | 91 |
| Treated | 56 | 56 | 91 |
| Completed | 0 | 0 | 0 |
| Not completed | 56 | 56 | 91 |
| Consent withdrawn by subject | - | 3 | - |
| Adverse event, non-fatal | 1 | - | 1 |
| Death | 33 | 40 | 49 |
| Not Specified | 5 | 1 | 8 |

| | | | |
|----------------------------------|----|---|----|
| Study terminated by sponsor | 12 | 8 | 30 |
| Lost to follow-up | 3 | 4 | 2 |
| Objective progression or relapse | 2 | - | 1 |

| Number of subjects in period 1 | Discontinued Prior to Randomization |
|---------------------------------------|--|
| Started | 10 |
| Treated | 10 |
| Completed | 0 |
| Not completed | 10 |
| Consent withdrawn by subject | 5 |
| Adverse event, non-fatal | - |
| Death | 4 |
| Not Specified | - |
| Study terminated by sponsor | - |
| Lost to follow-up | 1 |
| Objective progression or relapse | - |

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Active Titration Arm |
| Reporting group description: Participants initially received axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID). | |
| Reporting group title | Placebo Titration Arm |
| Reporting group description: Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID). | |
| Reporting group title | Non-randomized Arm |
| Reporting group description: Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm. | |
| Reporting group title | Discontinued Prior to Randomization |
| Reporting group description: Participants who discontinued before they were randomized to any of the treatment or non-randomized arms. | |

| Reporting group values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm |
|--|----------------------|-----------------------|--------------------|
| Number of subjects | 56 | 56 | 91 |
| Age Categorical Units: Subjects | | | |
| < 65 Years | 38 | 38 | 54 |
| >= 65 Years | 18 | 18 | 37 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 59.7 | 59.6 | 62.9 |
| standard deviation | ± 10.2 | ± 10.5 | ± 8.9 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 19 | 11 | 36 |
| Male | 37 | 45 | 55 |

| Reporting group values | Discontinued Prior to Randomization | Total | |
|------------------------------------|-------------------------------------|-------|--|
| Number of subjects | 10 | 213 | |
| Age Categorical Units: Subjects | | | |
| < 65 Years | 6 | 136 | |
| >= 65 Years | 4 | 77 | |

| | | | |
|---|---------------|-----|--|
| Age Continuous Units: Years arithmetic mean standard deviation | 62.9 ± 7.5 | - | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 4 | 70 | |
| Male | 6 | 143 | |

Subject analysis sets

| | |
|----------------------------|------------------|
| Subject analysis set title | All Participants |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All enrolled participants (randomized and non-randomized) who received at least one dose of study medication.

| | | | |
|---|------------------|--|--|
| Reporting group values | All Participants | | |
| Number of subjects | 213 | | |
| Age Categorical Units: Subjects | | | |
| < 65 Years | | | |
| ≥ 65 Years | | | |
| Age Continuous Units: Years arithmetic mean standard deviation | 61.2 ± 9.7 | | |
| Gender, Male/Female Units: Subjects | | | |
| Female | | | |
| Male | | | |

End points

End points reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Active Titration Arm |
| Reporting group description: Participants initially received axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID). | |
| Reporting group title | Placebo Titration Arm |
| Reporting group description: Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID). | |
| Reporting group title | Non-randomized Arm |
| Reporting group description: Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm. | |
| Reporting group title | Discontinued Prior to Randomization |
| Reporting group description: Participants who discontinued before they were randomized to any of the treatment or non-randomized arms. | |
| Subject analysis set title | All Participants |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All enrolled participants (randomized and non-randomized) who received at least one dose of study medication. | |

Primary: Objective Response Rate (ORR) - Percentage of Participants With Objective Response

| | |
|---|---|
| End point title | Objective Response Rate (ORR) - Percentage of Participants With Objective Response ^[1] |
| End point description: ORR was defined as the proportion of participants with objective response based assessment of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.0). CR was defined as complete disappearance of all target lesions and non-target disease. No new lesions. PR was defined as $\geq 30\%$ decrease on study under baseline of the sum of longest diameters of all target lesions. No unequivocal progression of non-target disease. No new lesions. | |
| End point type | Primary |
| End point timeframe: Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks. | |
| Notes: [1] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done. | |

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | All Participants |
|-----------------------------------|----------------------|-----------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 56 | 56 | 91 | 213 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 53.6 (39.7 to 67) | 33.9 (21.8 to 47.8) | 59.3 (48.5 to 69.5) | 48.4 (41.5 to 55.3) |

Statistical analyses

| Statistical analysis title | Objective Response Rate (ORR) |
|---|--|
| Statistical analysis description: | |
| ORR for the 2 treatment arms was compared with the Cochran-Mantel-Haenszel test stratified by ECOG performance status. The relative risk ratio estimator was used to contrast the treatment effects on the endpoint. Both a point estimate and a 2-sided 95% CI were calculated using a normal approximation. | |
| Comparison groups | Active Titration Arm v Placebo Titration Arm |
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0189 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.578 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.017 |
| upper limit | 2.448 |

Notes:

[2] - A priori defined threshold for statistical significance was: alpha=0.10 (one-sided)

Secondary: Progression-Free Survival (PFS)

| End point title | Progression-Free Survival (PFS) ^[3] |
|---|--|
| End point description: | |
| The time from first dose administration to first documentation of objective tumor progression or to death due to any cause. PFS in each arm was assessed using the Kaplan-Meier method and estimates of the PFS curves from the Kaplan-Meier method were presented. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks | |

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | All Participants |
|----------------------------------|----------------------|-----------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 56 | 56 | 91 | 213 |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.5 (9.2 to 24.5) | 15.7 (8.3 to 19.4) | 16.6 (11.2 to 22.5) | 14.6 (11.5 to 17.5) |

Statistical analyses

| Statistical analysis title | Progression-Free Survival (PFS) |
|---|--|
| Comparison groups | Active Titration Arm v Placebo Titration Arm |
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2444 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.849 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.535 |
| upper limit | 1.348 |

Secondary: Duration of Response (DR)

| | |
|------------------------|--|
| End point title | Duration of Response (DR) ^[4] |
| End point description: | DR was defined as the time from the first documentation of objective tumor response (complete response - CR or Partial response - PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. The median values were estimated based on Kaplan-Meier method. 95% confidence interval was based on the Brookmeyer and Crowley method. |
| End point type | Secondary |
| End point timeframe: | Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks |

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|----------------------------------|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 19 | 54 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (10.8 to | 21.2 (11.1 to | 23.3 (15.7 to | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

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|-----------------|--------------------------------------|
| End point title | Overall Survival (OS) ^[5] |
|-----------------|--------------------------------------|

End point description:

OS was defined as the time from date of the first dose of the study medication to date of death due to any cause. For participants who did not die, their survival times were to be censored at the last date they were known to be alive.

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

End point timeframe:

Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks.

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|----------------------------------|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 56 | 91 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 42.7 (24.7 to 9999) | 30.4 (23.7 to 45) | 41.6 (33 to 9999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Axitinib

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|-----------------|---|
| End point title | Maximum Observed Plasma Concentration (Cmax) of Axitinib ^[6] |
|-----------------|---|

End point description:

Cmax for steady-state axitinib was evaluated on Cycle 2 Day 15. Results were normalized to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm. Results were normalized to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm.

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

End point timeframe:

Cycle 2 Day 15 (C2D15): pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 20 | | |
| Units: ng/mL | | | | |
| geometric mean (confidence interval 95%) | 31.74 (21.63 to 46.58) | 23.05 (16.36 to 32.49) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) for Axitinib,

| | |
|---|---|
| End point title | Time to Reach Maximum Observed Plasma Concentration (Tmax) for Axitinib, ^[7] |
| End point description: | |
| Tmax for steady-state axitinib was evaluated on Cycle 2 Day 15. | |
| End point type | Secondary |
| End point timeframe: | |
| C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose | |

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|-------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 20 | | |
| Units: hrs | | | | |
| median (full range (min-max)) | 2.04 (1 to 6) | 2 (0 to 6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) for Axitinib

| | |
|-----------------|--|
| End point title | Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) for Axitinib ^[8] |
|-----------------|--|

End point description:

Area under the plasma concentration time-curve from zero to the last measurable concentration (AUClast). AUClast for steady-state axitinib was evaluated on Cycle 2 Day 15. Results were normalized

to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm.

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

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|--|--------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 20 | | |
| Units: ng.hr/mL | | | | |
| geometric mean (confidence interval 95%) | 105.33 (70.16 to 158.14) | 78.44 (54.53 to 112.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to 24 hours[AUC(0-24)] for Axitinib

| | |
|-----------------|--|
| End point title | Area Under the Curve From Time Zero to 24 hours[AUC(0-24)] for Axitinib ^[9] |
|-----------------|--|

End point description:

Area under the plasma concentration time-curve from zero 24 hours[AUC(0-24)]. AUC(0-24) for steady-state axitinib was evaluated on Cycle 2 Day 15. Results were normalized to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm.

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

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|--|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 14 | | |
| Units: ng.hr/mL | | | | |
| geometric mean (confidence interval 95%) | 258.68 (150.47 to 444.72) | 161.38 (102.09 to 255.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Decay Half-Life (t_{1/2}) for Axitinib

| | |
|--|---|
| End point title | Plasma Decay Half-Life (t _{1/2}) for Axitinib ^[10] |
| End point description: Plasma decay half-life is the time measured for the plasma concentration to decrease by one half. Plasma decay half life for steady-state axitinib was evaluated on Cycle 2 Day 15. | |
| End point type | Secondary |
| End point timeframe: C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose | |
| 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done. | |

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|--------------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 14 | | |
| Units: Hour | | | | |
| arithmetic mean (standard deviation) | 2.48 (± 1.902) | 2.81 (± 1.685) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent oral clearance (CL/F) of Axitinib

| | |
|---|--|
| End point title | Apparent oral clearance (CL/F) of Axitinib ^[11] |
| End point description: Clearance (CL) of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed (F). Clearance is defined as the volume of blood from which drug can be completely removed per unit of time. CL/F for steady-state axitinib was evaluated on Cycle 2 Day 15. | |
| End point type | Secondary |
| End point timeframe: C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose | |
| Notes: [11] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done. | |

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 14 | | |
| Units: L/hr | | | | |
| geometric mean (confidence interval 95%) | 54.15 (31.49 to 93.12) | 61.93 (39.17 to 97.91) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution during the elimination phase (V_z/F) for Axitinib

| | |
|-----------------|---|
| End point title | Apparent volume of distribution during the elimination phase (V _z /F) for Axitinib ^[12] |
|-----------------|---|

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. V_z/F is influenced by the fraction absorbed. V_z/F for steady-state axitinib was evaluated on Cycle 2 Day 15.

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

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[12] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | | |
|--|--------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 14 | | |
| Units: Litre | | | | |
| geometric mean (confidence interval 95%) | 158.18 (98.38 to 254.34) | 216.62 (145 to 323.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in systolic blood pressure

| | |
|-----------------|---|
| End point title | Change from baseline in systolic blood pressure ^[13] |
|-----------------|---|

End point description:

Value at respective visit minus value at baseline

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

End point timeframe:

At screening (D-14 to D-1); lead-in period: Cycle 1 - Day 1 and Day 15; Cycle 2 - Day 1 and Day 15; Cycle 3 & subsequent cycles Day 1; end of study and follow-up 28 days after last dose.

Notes:

[13] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|--------------------------------------|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 56 | 91 | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=52,51,73) | -4.3 (± 11.1) | -2.9 (± 9.2) | -1.8 (± 14.2) | |
| Cycle 1 Day 15 (n=56,56,91) | 3.8 (± 12.2) | 4.1 (± 12.5) | 11.5 (± 18) | |
| Cycle 2 Day 1 (n=56,56,91) | 1.9 (± 12.4) | 0.9 (± 13.6) | 9.9 (± 18.7) | |
| Cycle 2 Day 15 (n=55,55,86) | 3.6 (± 13.8) | 2.7 (± 16.6) | 5.9 (± 20.3) | |
| Cycle 3 Day 1 (n=48,49,84) | 3.5 (± 15.1) | 8.4 (± 15.4) | 5.2 (± 20.2) | |
| Cycle 4 Day 1 (n=45,48,79) | 4.3 (± 12.7) | 3.5 (± 13) | 5.5 (± 18.2) | |
| End of treatment (n=35,44,51) | 2.4 (± 17) | 1.7 (± 14) | -2.8 (± 19) | |
| Follow-up (n=16,25,36) | -3.6 (± 16.9) | -0.4 (± 16.3) | -0.6 (± 16.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in diastolic blood pressure

| | |
|--|--|
| End point title | Change from baseline in diastolic blood pressure ^[14] |
| End point description: | |
| Value at respective visit minus value at baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| At screening (D-14 to D-1); lead-in period: Cycle 1 - Day 1 and Day 15; Cycle 2 - Day 1 and Day 15; Cycle 3 & subsequent cycles Day 1; end of study and follow-up 28 days after last dose. | |

Notes:

[14] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|--------------------------------------|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 56 | 91 | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=52,51,73) | -1.6 (± 8.2) | -2.6 (± 7.4) | 0.5 (± 8.4) | |
| Cycle 1 Day 15 (n=56,56,91) | 4.8 (± 8.5) | 3 (± 7.7) | 11.5 (± 10) | |
| Cycle 2 Day 1 (n=56,56,91) | 4.2 (± 9) | 3.5 (± 8) | 10.5 (± 10.5) | |
| Cycle 2 Day 15 (n=55,55,86) | 5.5 (± 10.5) | 4.4 (± 10.7) | 9.7 (± 11.3) | |
| Cycle 3 Day 1 (n=48,49,84) | 6.6 (± 8.3) | 5.9 (± 9.3) | 9.1 (± 13.6) | |
| Cycle 4 Day 1 (n=45,48,79) | 7.4 (± 8.2) | 4.6 (± 8.5) | 8.7 (± 11.8) | |

| | | | | |
|-------------------------------|---------------|--------------|------------|--|
| End of treatment (n=35,44,51) | 0.6 (± 10.8) | 3.5 (± 6.3) | 3 (± 10.5) | |
| Follow-up (n=16,25,36) | -4.5 (± 10.1) | -1.3 (± 8.5) | 1.8 (± 9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Circulating Endothelial Cells (CECs) in blood: cluster of differentiation (CD)146+/CD105+ at baseline

| | |
|-----------------|---|
| End point title | Comparison of Circulating Endothelial Cells (CECs) in blood: cluster of differentiation (CD)146+/CD105+ at baseline ^[15] |
|-----------------|---|

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD146+/CD105+ CECs, CD146+/CD105+ mean fluorescence intensity (MFI) platelet derived growth factor receptor (PDGFR)-beta, CD146+/CD105+ MFI phospho-PDGFR (pPDGFR)-beta, CD146+/CD105+ phospho-Vascular endothelial growth factor receptor (pVEGFR), CD146+/CD105+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

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

End point timeframe:

At baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[15] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|---|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 22 | 20 | |
| Units: Fluorescent Intensity Unit (FIU) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline CECs Count (n=17,22,20) | 23584 (± 18213.1) | 28544 (± 27694.4) | 29663 (± 30651) | |
| Baseline MFI PDGFR-BETA (n=17,22,20) | 346815 (± 179563) | 455238 (± 238157) | 327567 (± 167728) | |
| Baseline MFI pPDGFR-BETA (n=17,22,20) | 401226 (± 195445) | 395509 (± 136933) | 397672 (± 193172) | |
| Baseline MFI pVEGFR (n=16,22,20) | 456086 (± 290174) | 436197 (± 128225) | 398754 (± 188137) | |
| Baseline MFI VEGFR (n=16,22,20) | 367799 (± 181320) | 473290 (± 228619) | 359092 (± 167706) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of the ratio of CECs in blood: CD146+/CD105+ at each time

point to baseline

| | |
|-----------------|--|
| End point title | Comparison of the ratio of CECs in blood: CD146+/CD105+ at each time point to baseline ^[16] |
|-----------------|--|

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD146+/CD105+ CECs, CD146+/CD105+ MFI platelet derived growth factor receptor (PDGFR)-beta, CD146+/CD105+ MFI phospho-PDGFR (pPDGFR)-beta, CD146+/CD105+ phospho-VEGFR (pVEGFR), CD146+/CD105+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

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

End point timeframe:

At end of the lead-in period (Cycle 1 Day 15), Cycle 2 Day 15 and End of therapy (EOT)

Notes:

[16] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|---|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 22 | 20 | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| C1D15:C1D1 CECs Count (n=11,18,14) | 2.3 (± 2.52) | 3.7 (± 6.92) | 2.2 (± 3.1) | |
| C2D15:C1D1 CECs Count (n=13,16,11) | 1.3 (± 1.43) | 4.4 (± 9.27) | 1.3 (± 1.22) | |
| EOT:C1D1 CECs Count (n=7,9,4) | 2.8 (± 4.81) | 8.9 (± 21.7) | 1.2 (± 1.5) | |
| C1D15:C1D1 MFI PDGFRBETA (n=11,17,13) | 1.3 (± 1.03) | 1.5 (± 1.14) | 1.1 (± 0.73) | |
| C2D15:C1D1 MFI PDGFRBETA (n=13,16,11) | 1.4 (± 1.24) | 1.1 (± 1.14) | 1.62 (± 1.62) | |
| EOT:C1D1 MFI PDGFRBETA (n=7,9,4) | 1.5 (± 1.75) | 0.6 (± 0.52) | 1.2 (± 1.78) | |
| C1D15:C1D1 MFI pPDGFR-BETA (n=11,17,13) | 1.1 (± 0.63) | 1.2 (± 0.77) | 1 (± 1.12) | |
| C2D15:C1D1 MFI pPDGFR-BETA (n=13,16,11) | 1 (± 0.69) | 0.8 (± 0.45) | 1.2 (± 0.79) | |
| EOT:C1D1 MFI pPDGFRBETA (n=7,9,4) | 0.8 (± 0.71) | 0.8 (± 0.93) | 1.9 (± 1.57) | |
| C1D15:C1D1 MFI pVEGFR (n=10,18,14) | 1 (± 0.46) | 1.2 (± 0.88) | 1.2 (± 1) | |
| C2D15:C1D1 MFI pVEGFR (n=12,16,11) | 1 (± 0.74) | 0.9 (± 0.82) | 1.2 (± 0.8) | |
| EOT:C1D1 MFI pVEGFR (n=7,9,4) | 0.8 (± 0.53) | 1.3 (± 0.96) | 3 (± 1.16) | |
| C1D15:C1D1 MFI VEGFR (n=10,18,14) | 1.4 (± 1.25) | 1.3 (± 0.94) | 1 (± 0.64) | |
| C2D15:C1D1 MFI VEGFR (n=12,16,11) | 1.5 (± 1.48) | 1.3 (± 0.99) | 2.1 (± 1.72) | |
| EOT:C1D1 MFI VEGFR (n=7,9,4) | 1.1 (± 1.03) | 0.7 (± 0.48) | 1.9 (± 1.63) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Endothelial Cells (CECs) in blood: CD31+/CD146+

| | |
|-----------------|--|
| End point title | Circulating Endothelial Cells (CECs) in blood: |
|-----------------|--|

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD31+/CD146+ CECs, CD31+/CD146+ MFI PDGFR-beta, CD31+/CD146+ MFI pPDGFR-beta, CD31+/CD146+ pVEGFR, CD31+/CD146+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

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

End point timeframe:

At baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[17] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|---|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 22 | 20 | |
| Units: Fluorescent Intensity Unit (FIU) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline CECs Count (n=17,22,20) | 74668 (± 50558.9) | 76258 (± 46779.5) | 77437 (± 63419.4) | |
| Baseline MFI PDGFR-BETA (n=17,21,20) | 333760 (± 164604) | 380886 (± 147261) | 442642 (± 267436) | |
| Baseline MFI pPDGFR-BETA (n=17,21,20) | 380139 (± 205600) | 355441 (± 147046) | 383202 (± 211174) | |
| Baseline MFI pVEGFR (n=17,22,20) | 385617 (± 203956) | 352644 (± 128803) | 380184 (± 173578) | |
| Baseline MFI VEGFR (n=17,22,20) | 330333 (± 151710) | 401909 (± 165235) | 359097 (± 146943) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of ratio of CECs in blood: CD31+/CD146+ at each time point to baseline

| | |
|-----------------|---|
| End point title | Comparison of ratio of CECs in blood: CD31+/CD146+ at each time point to baseline ^[18] |
|-----------------|---|

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD31+/CD146+ CECs, CD31+/CD146+ MFI PDGFR-beta, CD31+/CD146+ MFI pPDGFR-beta, CD31+/CD146+ pVEGFR, CD31+/CD146+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

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

End point timeframe:

At end of the lead-in period (Cycle 1 Day 15), Cycle 2 Day 15 and End of therapy (EOT)

Notes:

[18] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|---|----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 22 | 20 | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| C1D15:C1D1 CECs Count (n=11,18,14) | 2.7 (± 3.17) | 1.6 (± 2.32) | 1.5 (± 2.31) | |
| C2D15:C1D1 CECs Count (n=13,16,11) | 1.4 (± 1.4) | 2.2 (± 3.91) | 2.5 (± 3.98) | |
| EOT:C1D1 CECs COUNT (n=7,9,4) | 1.5 (± 1.95) | 1.4 (± 2.2) | 0.6 (± 0.71) | |
| C1D15:C1D1 MFI PDGFRBETA (n=11,15,13) | 1.2 (± 0.74) | 1.3 (± 0.89) | 0.8 (± 0.51) | |
| C2D15:C1D1 MFI PDGFRBETA (n=13,14,11) | 1.4 (± 1.36) | 1.1 (± 1.03) | 2.2 (± 2.64) | |
| EOT:C1D1 MFI PDGFRBETA (n=6,8,4) | 1.2 (± 1.23) | 0.6 (± 0.51) | 1.7 (± 1.49) | |
| C1D15:C1D1 MFI pPDGFR-BETA (n=11,15,13) | 1.2 (± 1.07) | 1.4 (± 0.81) | 1 (± 0.87) | |
| C2D15:C1D1 MFI pPDGFR-BETA (n=13,14,11) | 1.2 (± 0.89) | 0.8 (± 0.38) | 1.1 (± 0.71) | |
| EOT:C1D1 MFI pPDGFRBETA (n=6,8,4) | 0.7 (± 0.63) | 0.8 (± 0.91) | 3 (± 0.47) | |
| C1D15:C1D1 MFI pVEGFR (n=11,18,14) | 1.1 (± 0.75) | 1.4 (± 0.74) | 1.2 (± 0.9) | |
| C2D15:C1D1 MFI pVEGFR (n=13,16,10) | 1.2 (± 1) | 0.9 (± 0.68) | 1.3 (± 0.7) | |
| EOT:C1D1 MFI pVEGFR (n=7,9,4) | 0.7 (± 0.59) | 1.1 (± 1.24) | 3.1 (± 0.95) | |
| C1D15:C1D1 MFI VEGFR (n=11,18,14) | 1.3 (± 0.93) | 1.3 (± 0.9) | 1 (± 0.57) | |
| C2D15:C1D1 MFI VEGFR n=13,16,10) | 1.5 (± 1.44) | 1.2 (± 0.96) | 2.1 (± 1.8) | |
| EOT:C1D1 MFI VEGFR (n=7,9,4) | 1.2 (± 1.27) | 1.1 (± 0.9) | 1.5 (± 1.42) | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms

| | |
|-----------------|--|
| End point title | ORR in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms ^[19] |
|-----------------|--|

End point description:

ORR, defined as proportion of participants with CR or PR according to RECIST, in subgroups that were defined by VEGFA or VEGFR3 polymorphisms.

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

End point timeframe:

Baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[19] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|--|----------------------|-----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 49 | 79 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| VEGFA/rs699947 Genotype: A/A (n = 7, 9, 14) | 85.7 (42.1 to 99.6) | 22.2 (2.8 to 60) | 42.9 (17.7 to 71.1) | |
| VEGFA/rs699947 Genotype: A/C (n = 22, 20, 41) | 54.5 (32.2 to 75.6) | 35 (15.4 to 59.2) | 65.9 (49.4 to 79.9) | |
| VEGFA/rs699947 Genotype: C/C (n = 14, 14, 24) | 50 (23 to 77) | 35.7 (12.8 to 64.9) | 66.7 (44.7 to 84.4) | |
| VEGFA/rs1570360 Genotype: G/G (n = 22, 23, 43) | 59.1 (36.4 to 79.3) | 39.1 (19.7 to 61.5) | 67.4 (51.5 to 80.9) | |
| VEGFA/rs1570360 Genotype: G/A (n = 19, 16, 29) | 57.9 (33.5 to 79.7) | 18.8 (4 to 45.6) | 58.6 (38.9 to 76.5) | |
| VEGFA/rs1570360 Genotype: A/A (n = 2, 4, 7) | 50 (1.3 to 98.7) | 50 (6.8 to 93.2) | 42.9 (9.9 to 81.6) | |
| VEGFR3/rs448012 Genotype: G/G (n = 16, 15, 28) | 81.3 (54.4 to 96) | 53.3 (26.6 to 78.7) | 60.7 (40.6 to 78.5) | |
| VEGFR3/rs448012 Genotype: G/C (n = 22, 22, 35) | 45.5 (24.4 to 67.8) | 18.2 (5.2 to 40.3) | 57.1 (39.4 to 73.7) | |
| VEGFR3/rs448012 Genotype: C/C (n = 5, 6, 16) | 40 (5.3 to 85.3) | 33.3 (4.3 to 77.7) | 75 (47.6 to 92.7) | |
| VEGFR3/rs307826 Genotype: A/A (n = 36, 39, 79) | 58.3 (40.8 to 74.5) | 30.8 (17 to 47.6) | 64.3 (51.9 to 75.4) | |
| VEGFR3/rs307826 Genotype: A/G (n = 6, 4, 9) | 50 (11.8 to 88.2) | 50 (6.8 to 93.2) | 44.4 (13.7 to 78.8) | |
| VEGFR3/rs307826 Genotype: G/G (n = 1, 0, 0) | 100 (2.5 to 100) | 0 (0 to 0) | 0 (0 to 0) | |
| VEGFR3/rs307821 Genotype: G/G (n = 36, 38, 79) | 55.6 (38.1 to 72.1) | 28.9 (15.4 to 45.9) | 65.2 (52.8 to 76.3) | |
| VEGFR3/rs307821 Genotype: G/T (n = 6, 5, 10) | 66.7 (22.3 to 95.7) | 60 (14.7 to 94.7) | 40 (12.2 to 73.8) | |
| VEGFR3/rs307821 Genotype: T/T (n = 1, 0, 0) | 100 (2.5 to 100) | 0 (0 to 0) | 0 (0 to 0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms

| | |
|-----------------|--|
| End point title | PFS in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms ^[20] |
|-----------------|--|

End point description:

PFS, defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, in subgroups that were defined by VEGFA or VEGFR3 polymorphisms. Estimates of the PFS curves from the Kaplan-Meier method were presented.

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

End point timeframe:

Baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[20] - 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: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

| End point values | Active Titration Arm | Placebo Titration Arm | Non-randomized Arm | |
|--|-----------------------|-----------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 43 | 43 | 79 | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| VEGFA/rs699947 Genotype: A/A (n = 7, 9, 14) | 9999 (1.74 to 9999) | 11.5 (7.33 to 9999) | 7.33 (5.06 to 13.83) | |
| VEGFA/rs699947 Genotype: A/C (n = 22, 20, 41) | 11.07 (3.02 to 17.44) | 9.67 (1.91 to 16.59) | 16.59 (10.97 to 9999) | |
| VEGFA/rs699947 Genotype: C/C (n = 14, 14, 41) | 18.74 (1.84 to 9999) | 24.64 (4.01 to 9999) | 25.13 (8.28 to 30.45) | |
| VEGFA/rs1570360 Genotype: G/G (n = 22, 23, 43) | 14.62 (7.39 to 9999) | 19.42 (5.81 to 27.63) | 25.13 (11.47 to 30.45) | |
| VEGFA/rs1570360 Genotype: G/A (n = 19, 16, 29) | 12.78 (1.84 to 9999) | 8.34 (1.91 to 16.59) | 13.9 (8.28 to 22.54) | |
| VEGFA/rs1570360 Genotype: A/A (n = 2, 4, 29) | 9999 (1.74 to 9999) | 10.04 (3.58 to 9999) | 8.57 (1.74 to 9999) | |
| VEGFR3/rs448012 Genotype: G/G (n = 16, 15, 28) | 17.44 (12.78 to 9999) | 19.42 (5.35 to 9999) | 22.54 (8.08 to 9999) | |
| VEGFR3/rs448012 Genotype: G/C (n = 22, 22, 35) | 9.18 (1.84 to 9999) | 8.31 (3.58 to 16.52) | 13.83 (5.62 to 16.59) | |
| VEGFR3/rs448012 Genotype: C/C (n = 5, 6, 16) | 11.07 (1.84 to 9999) | 15.67 (1.91 to 27.63) | 9999 (8.57 to 9999) | |
| VEGFR3/rs307826 Genotype: A/A (n = 36, 39, 70) | 13.73 (8.28 to 24.47) | 15.67 (8.21 to 22.17) | 16.56 (10.28 to 25.13) | |
| VEGFR3/rs307826 Genotype: A/G (n = 6, 4, 9) | 16.52 (1.18 to 9999) | 7.93 (1.84 to 11.86) | 16.26 (2.66 to 30.45) | |
| VEGFR3/rs307826 Genotype: G/G (n = 0, 0, 0) | 0 (0 to 0) | 0 (0 to 0) | 0 (0 to 0) | |
| VEGFR3/rs307821 Genotype: G/G (n = 36, 38, 69) | 12.78 (7.39 to 24.47) | 15.67 (8.21 to 23.95) | 16.59 (10.28 to 28.52) | |
| VEGFR3/rs307821 Genotype: G/T (n = 36, 38, 10) | 24.8 (1.18 to 9999) | 8.34 (1.84 to 11.86) | 13.86 (2.66 to 30.45) | |
| VEGFR3/rs307821 Genotype: T/T (n = 1, 0, 0) | 0 (0 to 0) | 0 (0 to 0) | 0 (0 to 0) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Active Titration Arm |
|-----------------------|----------------------|

Reporting group description:

Participants initially received axitinib 5 mg twice a day (BID) + axitinib(blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

| | |
|-----------------------|--------------------|
| Reporting group title | Non-randomized Arm |
|-----------------------|--------------------|

Reporting group description:

Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

| | |
|-----------------------|-----------------------|
| Reporting group title | Placebo Titration Arm |
|-----------------------|-----------------------|

Reporting group description:

Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Discontinued Prior to Randomization |
|-----------------------|-------------------------------------|

Reporting group description:

Participants who were discontinued prior to randomization to either treatment or non-randomization arms.

| Serious adverse events | Active Titration Arm | Non-randomized Arm | Placebo Titration Arm |
|---|----------------------|--------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 56 (44.64%) | 39 / 91 (42.86%) | 14 / 56 (25.00%) |
| number of deaths (all causes) | 4 | 0 | 1 |
| number of deaths resulting from adverse events | 3 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Breast cancer | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Surgical and medical procedures | | | |
| Incisional hernia repair | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 | | | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 6 / 91 (6.59%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 2 / 56 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Pelvic prolapse | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Dyspnoea | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 hypertension | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Hypercapnia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|----------------|----------------|----------------|
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Postoperative hernia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Postoperative ileus | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 91 (2.20%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Myocardial infarction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 4 / 56 (7.14%) | 2 / 91 (2.20%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Nervous system disorders | | | |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Syncope | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Monoparesis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Tinnitus | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 91 (3.30%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 91 (0.00%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Ascites | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 2 / 56 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Ileus | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Small intestinal obstruction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Postrenal failure | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 failure | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 0 / 56 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 retention | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 91 (2.20%) | 0 / 56 (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 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| 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 | | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 91 (1.10%) | 2 / 56 (3.57%) |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Gingivitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 3 / 91 (3.30%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 3 / 7 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 91 (2.20%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 0 / 56 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 0 / 56 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-------------------------------------|--|--|
| Serious adverse events | Discontinued Prior to Randomization | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |

| | | | |
|--|----------------------------------|--|--|
| Incisional hernia repair subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| General disorders and administration site conditions Disease progression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| General physical health deterioration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Chest pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Fatigue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Pyrexia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Reproductive system and breast disorders Pelvic prolapse subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders Atelectasis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercapnia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Delirium | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative hernia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative ileus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diastolic dysfunction | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Monoparesis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Abdominal pain | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain upper | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ascites | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Crohn's disease | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal hypomotility | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 10 (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 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postrenal failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Renal failure | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 10 (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 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cystitis | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung abscess | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis bacterial | | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative wound infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 10 (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 | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 10 (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 | Active Titration Arm | Non-randomized Arm | Placebo Titration Arm |
|---|----------------------|--------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 56 (98.21%) | 91 / 91 (100.00%) | 51 / 56 (91.07%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 35 / 56 (62.50%) | 76 / 91 (83.52%) | 24 / 56 (42.86%) |
| occurrences (all) | 67 | 167 | 75 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 9 / 91 (9.89%) | 8 / 56 (14.29%) |
| occurrences (all) | 0 | 10 | 11 |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 91 (1.10%) | 3 / 56 (5.36%) |
| occurrences (all) | 0 | 1 | 3 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 6 / 91 (6.59%) | 5 / 56 (8.93%) |
| occurrences (all) | 9 | 11 | 7 |
| Fatigue | | | |
| subjects affected / exposed | 27 / 56 (48.21%) | 49 / 91 (53.85%) | 26 / 56 (46.43%) |
| occurrences (all) | 74 | 127 | 66 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 91 (0.00%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 12 / 56 (21.43%) | 13 / 91 (14.29%) | 8 / 56 (14.29%) |
| occurrences (all) | 21 | 39 | 21 |
| Chest pain | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 6 / 91 (6.59%) | 2 / 56 (3.57%) |
| occurrences (all) | 8 | 6 | 2 |
| Chills | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 5 / 91 (5.49%) | 1 / 56 (1.79%) |
| occurrences (all) | 4 | 5 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 14 / 91 (15.38%) | 3 / 56 (5.36%) |
| occurrences (all) | 11 | 29 | 3 |

| | | | |
|---|------------------|------------------|------------------|
| Pain | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 6 / 91 (6.59%) | 3 / 56 (5.36%) |
| occurrences (all) | 5 | 9 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 4 / 91 (4.40%) | 3 / 56 (5.36%) |
| occurrences (all) | 8 | 4 | 4 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 19 / 91 (20.88%) | 8 / 56 (14.29%) |
| occurrences (all) | 8 | 25 | 13 |
| Dysphonia | | | |
| subjects affected / exposed | 18 / 56 (32.14%) | 44 / 91 (48.35%) | 20 / 56 (35.71%) |
| occurrences (all) | 27 | 74 | 20 |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 27 / 91 (29.67%) | 8 / 56 (14.29%) |
| occurrences (all) | 15 | 36 | 11 |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 12 / 91 (13.19%) | 3 / 56 (5.36%) |
| occurrences (all) | 5 | 24 | 3 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 8 / 91 (8.79%) | 2 / 56 (3.57%) |
| occurrences (all) | 5 | 9 | 2 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 91 (0.00%) | 1 / 56 (1.79%) |
| occurrences (all) | 1 | 0 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 8 / 91 (8.79%) | 4 / 56 (7.14%) |
| occurrences (all) | 4 | 10 | 4 |
| Anxiety | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 7 / 91 (7.69%) | 3 / 56 (5.36%) |
| occurrences (all) | 4 | 10 | 3 |
| Depression | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 6 / 91 (6.59%) | 4 / 56 (7.14%) |
| occurrences (all) | 5 | 8 | 4 |
| Delirium | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 91 (0.00%) 0 | 0 / 56 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 56 (10.71%) 10 | 12 / 91 (13.19%) 36 | 9 / 56 (16.07%) 21 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 56 (10.71%) 10 | 12 / 91 (13.19%) 36 | 10 / 56 (17.86%) 23 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 10 | 14 / 91 (15.38%) 31 | 8 / 56 (14.29%) 17 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 24 | 10 / 91 (10.99%) 23 | 7 / 56 (12.50%) 17 |
| Fibrin D dimer increased subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 91 (0.00%) 0 | 1 / 56 (1.79%) 2 |
| Weight decreased subjects affected / exposed occurrences (all) | 16 / 56 (28.57%) 53 | 25 / 91 (27.47%) 88 | 12 / 56 (21.43%) 22 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 4 | 6 / 91 (6.59%) 12 | 4 / 56 (7.14%) 5 |
| Blood glucose decreased subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 10 | 1 / 91 (1.10%) 1 | 5 / 56 (8.93%) 7 |
| Blood potassium increased subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 30 | 4 / 91 (4.40%) 5 | 3 / 56 (5.36%) 17 |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 3 | 5 / 91 (5.49%) 17 | 2 / 56 (3.57%) 3 |
| Haemoglobin decreased | | | |

| | | | |
|--|-----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 5 / 91 (5.49%) 14 | 1 / 56 (1.79%) 6 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 1 / 91 (1.10%) 8 | 3 / 56 (5.36%) 4 |
| Blood sodium decreased subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 4 | 1 / 91 (1.10%) 2 | 3 / 56 (5.36%) 5 |
| Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 34 | 9 / 91 (9.89%) 15 | 7 / 56 (12.50%) 10 |
| Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 91 (0.00%) 0 | 1 / 56 (1.79%) 0 |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) | 9 / 56 (16.07%) 15 | 21 / 91 (23.08%) 31 | 5 / 56 (8.93%) 10 |
| Dyskinesia subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 91 (0.00%) 0 | 0 / 56 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 9 / 56 (16.07%) 18 | 27 / 91 (29.67%) 53 | 15 / 56 (26.79%) 25 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 4 / 91 (4.40%) 5 | 0 / 56 (0.00%) 0 |
| Paraesthesia subjects affected / exposed occurrences (all) | 5 / 56 (8.93%) 8 | 3 / 91 (3.30%) 3 | 3 / 56 (5.36%) 4 |
| Transient ischaemic attack subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 1 / 91 (1.10%) 1 | 0 / 56 (0.00%) 0 |
| Dizziness | | | |

| | | | |
|---|-------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 14 | 14 / 91 (15.38%) 53 | 10 / 56 (17.86%) 16 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 6 | 3 / 91 (3.30%) 4 | 1 / 56 (1.79%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 5 / 56 (8.93%) 5 | 9 / 91 (9.89%) 13 | 4 / 56 (7.14%) 6 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 2 / 91 (2.20%) 0 | 0 / 56 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 5 / 56 (8.93%) 8 | 15 / 91 (16.48%) 22 | 3 / 56 (5.36%) 5 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 4 / 91 (4.40%) 4 | 3 / 56 (5.36%) 4 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 9 / 56 (16.07%) 26 | 11 / 91 (12.09%) 17 | 9 / 56 (16.07%) 10 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 56 (10.71%) 9 | 11 / 91 (12.09%) 14 | 2 / 56 (3.57%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 11 / 56 (19.64%) 15 | 27 / 91 (29.67%) 43 | 7 / 56 (12.50%) 11 |
| Diarrhoea subjects affected / exposed occurrences (all) | 34 / 56 (60.71%) 232 | 58 / 91 (63.74%) 236 | 35 / 56 (62.50%) 97 |
| Dry Mouth subjects affected / exposed occurrences (all) | 7 / 56 (12.50%) 9 | 7 / 91 (7.69%) 8 | 2 / 56 (3.57%) 2 |
| Dyspepsia | | | |

| | | | |
|----------------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 7 / 56 (12.50%) | 18 / 91 (19.78%) | 5 / 56 (8.93%) |
| occurrences (all) | 10 | 24 | 5 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 91 (2.20%) | 2 / 56 (3.57%) |
| occurrences (all) | 0 | 3 | 2 |
| Flatulence | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 4 / 91 (4.40%) | 3 / 56 (5.36%) |
| occurrences (all) | 7 | 7 | 3 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 91 (4.40%) | 1 / 56 (1.79%) |
| occurrences (all) | 2 | 8 | 1 |
| Nausea | | | |
| subjects affected / exposed | 24 / 56 (42.86%) | 33 / 91 (36.26%) | 19 / 56 (33.93%) |
| occurrences (all) | 70 | 66 | 57 |
| Stomatitis | | | |
| subjects affected / exposed | 10 / 56 (17.86%) | 17 / 91 (18.68%) | 4 / 56 (7.14%) |
| occurrences (all) | 18 | 26 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 18 / 56 (32.14%) | 25 / 91 (27.47%) | 12 / 56 (21.43%) |
| occurrences (all) | 35 | 44 | 37 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 6 / 91 (6.59%) | 0 / 56 (0.00%) |
| occurrences (all) | 2 | 9 | 2 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 91 (3.30%) | 3 / 56 (5.36%) |
| occurrences (all) | 1 | 5 | 3 |
| Gastritis | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 9 / 91 (9.89%) | 2 / 56 (3.57%) |
| occurrences (all) | 3 | 13 | 3 |
| Toothache | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 5 / 91 (5.49%) | 3 / 56 (5.36%) |
| occurrences (all) | 1 | 16 | 5 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 6 / 91 (6.59%) | 3 / 56 (5.36%) |
| occurrences (all) | 2 | 6 | 3 |
| Proctalgia | | | |

| | | | |
|--|------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 5 / 91 (5.49%) 7 | 0 / 56 (0.00%) 0 |
| Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 4 | 5 / 91 (5.49%) 9 | 1 / 56 (1.79%) 1 |
| Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) | 7 / 56 (12.50%) 7 | 7 / 91 (7.69%) 8 | 3 / 56 (5.36%) 3 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 18 / 56 (32.14%) 37 | 40 / 91 (43.96%) 199 | 10 / 56 (17.86%) 45 |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 7 | 13 / 91 (14.29%) 16 | 6 / 56 (10.71%) 9 |
| Rash subjects affected / exposed occurrences (all) | 5 / 56 (8.93%) 8 | 19 / 91 (20.88%) 30 | 8 / 56 (14.29%) 11 |
| Alopecia subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 14 / 91 (15.38%) 14 | 3 / 56 (5.36%) 3 |
| Erythema subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 6 / 91 (6.59%) 6 | 2 / 56 (3.57%) 2 |
| Hyperkeratosis subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 5 / 91 (5.49%) 8 | 4 / 56 (7.14%) 5 |
| Renal and urinary disorders Haemoglobinuria subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 3 | 5 / 91 (5.49%) 6 | 3 / 56 (5.36%) 4 |
| Proteinuria subjects affected / exposed occurrences (all) | 12 / 56 (21.43%) 41 | 40 / 91 (43.96%) 376 | 12 / 56 (21.43%) 43 |
| Dysuria | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 5 | 3 / 91 (3.30%) 5 | 0 / 56 (0.00%) 0 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 18 / 56 (32.14%) 26 | 41 / 91 (45.05%) 64 | 13 / 56 (23.21%) 15 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 13 / 56 (23.21%) 23 | 17 / 91 (18.68%) 33 | 11 / 56 (19.64%) 53 |
| Back pain subjects affected / exposed occurrences (all) | 13 / 56 (23.21%) 32 | 17 / 91 (18.68%) 28 | 8 / 56 (14.29%) 12 |
| Groin pain subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 1 / 91 (1.10%) 2 | 0 / 56 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 8 | 15 / 91 (16.48%) 17 | 4 / 56 (7.14%) 6 |
| Bone pain subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 5 / 91 (5.49%) 7 | 2 / 56 (3.57%) 2 |
| Flank pain subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 4 / 91 (4.40%) 4 | 3 / 56 (5.36%) 3 |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 4 | 6 / 91 (6.59%) 23 | 3 / 56 (5.36%) 3 |
| Muscular weakness subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 4 | 2 / 91 (2.20%) 2 | 2 / 56 (3.57%) 2 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 8 | 15 / 91 (16.48%) 17 | 4 / 56 (7.14%) 6 |
| Musculoskeletal stiffness | | | |

| | | | |
|---|------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 3 / 91 (3.30%) 4 | 4 / 56 (7.14%) 13 |
| Myalgia subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 6 | 8 / 91 (8.79%) 17 | 3 / 56 (5.36%) 34 |
| Neck pain subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 10 | 5 / 91 (5.49%) 8 | 4 / 56 (7.14%) 5 |
| Pain in extremity subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 11 | 23 / 91 (25.27%) 26 | 9 / 56 (16.07%) 13 |
| Infections and infestations | | | |
| Rhinitis subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 7 | 4 / 91 (4.40%) 5 | 6 / 56 (10.71%) 6 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 6 | 10 / 91 (10.99%) 20 | 1 / 56 (1.79%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 8 | 19 / 91 (20.88%) 37 | 3 / 56 (5.36%) 6 |
| Sinusitis subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 8 | 2 / 91 (2.20%) 2 | 2 / 56 (3.57%) 3 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 6 | 6 / 91 (6.59%) 6 | 3 / 56 (5.36%) 4 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 0 / 91 (0.00%) 0 | 3 / 56 (5.36%) 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 21 / 56 (37.50%) 45 | 37 / 91 (40.66%) 109 | 16 / 56 (28.57%) 28 |
| Dehydration | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 56 (5.36%) | 5 / 91 (5.49%) | 4 / 56 (7.14%) |
| occurrences (all) | 3 | 8 | 6 |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 4 / 91 (4.40%) | 1 / 56 (1.79%) |
| occurrences (all) | 6 | 9 | 2 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 6 / 91 (6.59%) | 3 / 56 (5.36%) |
| occurrences (all) | 4 | 8 | 7 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 5 / 91 (5.49%) | 1 / 56 (1.79%) |
| occurrences (all) | 7 | 6 | 1 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 7 / 91 (7.69%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 12 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 9 / 91 (9.89%) | 0 / 56 (0.00%) |
| occurrences (all) | 1 | 17 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 2 / 91 (2.20%) | 1 / 56 (1.79%) |
| occurrences (all) | 7 | 4 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 91 (2.20%) | 3 / 56 (5.36%) |
| occurrences (all) | 0 | 2 | 3 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 91 (4.40%) | 2 / 56 (3.57%) |
| occurrences (all) | 2 | 15 | 3 |

| | | | |
|---|-------------------------------------|--|--|
| Non-serious adverse events | Discontinued Prior to Randomization | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 10 (90.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 10 (50.00%) | | |
| occurrences (all) | 12 | | |
| Hypotension | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) General physical health deterioration subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 4 / 10 (40.00%) 7 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Dysphonia subjects affected / exposed occurrences (all) | 3 / 10 (30.00%) 3 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 3 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Depression subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Delirium subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 2 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Aspartate aminotransferase increased | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 3 | | |
| Fibrin D dimer increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood thyroid stimulating hormone | | | |

| | | | |
|--|--|--|--|
| increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | | |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Dyskinesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Transient ischaemic attack subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia | 1 / 10 (10.00%) 1 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | | |
| occurrences (all) | 4 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Dry Mouth | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemorrhoids | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 4 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Haemoglobinuria | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Proteinuria | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Groin pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|----------------------|--|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 4 | | |
| Infections and infestations | | | |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 10 (30.00%) 3 | | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported