



Clinical trial results:

A Multicenter, Randomized, Double-Blind Phase 2 Trial of Lenvatinib (E7080) in Subjects With 131I-Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 18 mg Daily Will Provide Comparable Efficacy to a 24-mg Starting Dose, But Have a Better Safety Profile

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-005199-27 |
| Trial protocol | BE DE DK ES FR IT |
| Global end of trial date | 10 September 2020 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 26 September 2021 |
| First version publication date | 26 September 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | E7080-G000-211 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02702388 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eisai Ltd. |
| Sponsor organisation address | European Knowledge Centre, Mosquito Way, Hatfield, United Kingdom, AL10 9SN |
| Public contact | Eisai Medical Information, Eisai Inc., 1 888-274-2378, esi_oncmedinfo@eisai.com |
| Scientific contact | Eisai Medical Information, Eisai Inc., 1 888-274-2378, esi_oncmedinfo@eisai.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | |
| 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 | 10 September 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 September 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine whether a starting dose of lenvatinib 18 milligram (mg), once daily (QD) will provide comparable efficacy (based on objective response rate at week 24 [ORR24wk]) with an improved safety profile compared to 24 mg QD (based on treatment-emergent adverse events [TEAEs] of Grade 3 or higher in the first 24 weeks after randomization).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 08 June 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Canada: 10 |
| Country: Number of subjects enrolled | France: 32 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Korea, Republic of: 20 |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | United States: 54 |
| Worldwide total number of subjects | 152 |
| EEA total number of subjects | 42 |

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) | 71 |
| From 65 to 84 years | 78 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 38 investigative sites in the North America, Europe, Russia, Australia, and Asia. As planned, the study was unblinded after the primary analysis was completed and all subjects were treated with open-label lenvatinib at their current dose level at the discretion of the investigator.

Pre-assignment

Screening details:

A total of 241 subjects were screened and enrolled of which 89 subjects were screen failures, and 152 subjects were randomized and treated.

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 |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Lenvatinib 24 mg |

Arm description:

Subjects received lenvatinib 24 mg, capsule, orally, once daily in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subjects received a total of 4 capsules in the form of two 10-mg capsules and one 4-mg capsule containing lenvatinib and one 4-mg placebo capsule.

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenvatinib |
| Investigational medicinal product code | |
| Other name | E7080, LENVIMA |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Lenvatinib 24 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months).

| | |
|------------------|------------------|
| Arm title | Lenvatinib 18 mg |
|------------------|------------------|

Arm description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subjects received a total of 4 capsules in the form of one 10-mg capsule and two 4-mg capsules containing lenvatinib and one 10-mg placebo capsule.

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenvatinib |
| Investigational medicinal product code | |
| Other name | E7080, LENVIMA |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Lenvatinib 18 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months).

| Number of subjects in period 1 | Lenvatinib 24 mg | Lenvatinib 18 mg |
|---------------------------------------|------------------|------------------|
| Started | 75 | 77 |
| Completed | 35 | 26 |
| Not completed | 40 | 51 |
| Consent withdrawn by subject | 9 | 7 |
| Unspecified | 2 | 4 |
| Adverse Events | 11 | 15 |
| Disease Progression | 18 | 25 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Lenvatinib 24 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received lenvatinib 24 mg, capsule, orally, once daily in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subjects received a total of 4 capsules in the form of two 10-mg capsules and one 4-mg capsule containing lenvatinib and one 4-mg placebo capsule.

| | |
|-----------------------|------------------|
| Reporting group title | Lenvatinib 18 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subjects received a total of 4 capsules in the form of one 10-mg capsule and two 4-mg capsules containing lenvatinib and one 10-mg placebo capsule.

| Reporting group values | Lenvatinib 24 mg | Lenvatinib 18 mg | Total |
|---|------------------|------------------|-------|
| Number of subjects | 75 | 77 | 152 |
| Age Categorical Units: Subjects | | | |
| Adults (18-64 years) | 35 | 36 | 71 |
| From 65-84 years | 39 | 39 | 78 |
| 85 years and over | 1 | 2 | 3 |
| Age Continuous Units: years | | | |
| median | 64.3 | 64.4 | - |
| standard deviation | ± 10.58 | ± 11.79 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 34 | 40 | 74 |
| Male | 41 | 37 | 78 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 3 | 4 | 7 |
| Not Hispanic or Latino | 71 | 67 | 138 |
| Unknown or Not Reported | 1 | 6 | 7 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 11 | 11 | 22 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 3 | 2 | 5 |
| White | 46 | 40 | 86 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 15 | 23 | 38 |

End points

End points reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Lenvatinib 24 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received lenvatinib 24 mg, capsule, orally, once daily in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subjects received a total of 4 capsules in the form of two 10-mg capsules and one 4-mg capsule containing lenvatinib and one 4-mg placebo capsule.

| | |
|-----------------------|------------------|
| Reporting group title | Lenvatinib 18 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subjects received a total of 4 capsules in the form of one 10-mg capsule and two 4-mg capsules containing lenvatinib and one 10-mg placebo capsule.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Pooled Lenvatinib 24 mg |
|----------------------------|-------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All subjects received lenvatinib 24 mg, capsule orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first in studies E7080-G000-303 (NCT01321554), E7080-G000-201 (NCT00784303) and this current study (E7080-G000-211).

| | |
|----------------------------|------------------------------|
| Subject analysis set title | Pooled Lenvatinib or Placebo |
|----------------------------|------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All subject who received lenvatinib 24 mg or 18 mg or placebo, capsule, orally, once daily in a 28-day treatment cycles until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first in study E7080-G000-303 (NCT01321554) and current study (E7080-G000-211).

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Pooled Lenvatinib or Placebo: PFS |
|----------------------------|-----------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All subject received lenvatinib 24 mg or 18 mg or placebo, capsule orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first in study E7080-G000-303 (NCT01321554) and current study (E7080-G000-211).

| | |
|----------------------------|--------------------------------------|
| Subject analysis set title | Pooled Lenvatinib or Placebo: Safety |
|----------------------------|--------------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All subjects received lenvatinib 24 mg or 18 mg or placebo, capsule orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first in studies E7080-G000-303 (NCT01321554), E7080-G000-201 (NCT00784303) and this current study (E7080-G000-211) with available pharmacokinetic data.

Primary: Objective Response Rate (ORR) as of Week 24 (ORR24wk)

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) as of Week 24 (ORR24wk) |
|-----------------|---|

End point description:

ORR as of Week 24 was defined as the percentage of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) as of the Week 24 time point or earlier, as measured by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). CR: was disappearance of all

target lesions. Any pathological lymph nodes (target or non-target) had to be reduced in short axis to less than (<) 10 millimeter (mm). PR: was at least a 30 percent (%) decrease in sum of diameter (SOD) of target lesions, taking as reference the baseline SOD. Full analysis set (FAS) included all subjects randomly assigned to treatment.

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: | |
| From the date of randomization up to Week 24 | |

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 57.3 (46.1 to 68.5) | 40.3 (29.3 to 51.2) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Lenvatinib 24 mg, Lenvatinib 18 mg |
|----------------------------|------------------------------------|

Statistical analysis description:

Odds ratio of ORR as of Week 24 response (18 mg vs 24 mg) along with its 95% confidence interval (CI) using the Cochran-Mantel-Haenszel (CMH) method, stratified by the randomization stratification factors. The test was performed per the 95% CI using the noninferiority margin of 0.4. Noninferiority will be declared if the lower limit of the 95% CI for the odds ratio is greater than 0.4.

| | |
|---|-------------------------------------|
| Comparison groups | Lenvatinib 18 mg v Lenvatinib 24 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 99999 [1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 0.96 |

Notes:

[1] - Here 99999 signifies that no p-value was calculated.

Primary: Percentage of Subjects With Grade 3 or Higher Treatment-emergent Adverse Events (TEAEs) in the First 24 Weeks

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Grade 3 or Higher Treatment-emergent Adverse Events (TEAEs) in the First 24 Weeks ^[2] |
|-----------------|--|

End point description:

This outcome measure reports TEAEs in the first 24 weeks only. A TEAE was defined as any adverse event (AE) that had an onset date on or after the first dose of study drug up to 28 days following the last dose of study drug, or a worsening in severity from Baseline (pretreatment). In addition, if an AE reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, it was also counted as a TEAE. A severity grade was defined by the Common Terminology

Criteria for Adverse Events (CTCAE) Version 4.03. As per CTCAE, Grade 1 scales as Mild; Grade 2 scales as Moderate; Grade 3 scales as severe or medically significant but not immediately life threatening; Grade 4 scales as life-threatening consequences; and Grade 5 scales as death related to AE. Safety analysis set included all subjects randomly assigned to treatment and who received at least 1 dose of study drug.

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

End point timeframe:

Baseline up to Week 24

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|-------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 61.3 | 57.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression-free survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS, defined as the time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first, as measured by RECIST V1.1. PD: 20% increase in the sum of the pertinent diameters (SOD) of target lesions, taking as reference the smallest sum SOD recorded since the treatment started or the appearance of one or more new lesions. PFS was analyzed using the Kaplan-Meier method. FAS included all subjects randomly assigned to treatment. Here, '99999' signifies that median and maximum range of 95% CI was not estimable because insufficient number of subjects had events. As planned, data for this endpoint was analyzed and collected till Primary completion date.

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

End point timeframe:

Time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first up to approximately 2 years 6 months

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (22.1 to 99999) | 24.4 (14.7 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PFS after next line of treatment (PFS2)

| | |
|-----------------|---|
| End point title | PFS after next line of treatment (PFS2) |
|-----------------|---|

End point description:

PFS2, defined as the time from randomization to PD on next-line treatment, or death from any cause, whichever occurred first, as measured by RECIST V1.1. PD: 20% increase in the SOD of target lesions, taking as reference the smallest sum SOD recorded since the treatment started or the appearance of one or more new lesions. PFS was analyzed using the Kaplan-Meier method. FAS included all subjects randomly assigned to treatment. Here '99999' signifies that median and 95% CI was not estimable because insufficient number of subjects had events. As planned, data for this endpoint was analyzed and collected till Primary completion date.

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

End point timeframe:

Time from randomization to PD on next-line treatment or death from any cause, whichever occurs first up to approximately 2 years 6 months

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|----------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (22.1 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With TEAE and Serious Adverse Events (SAEs)

| | |
|-----------------|--|
| End point title | Number of Subjects With TEAE and Serious Adverse Events (SAEs) |
|-----------------|--|

End point description:

TEAEs were defined as those AEs that occurred (or worsened, if present at Baseline) after the first dose of study drug through 28 days after the last dose of study drug. An AE was defined as any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with medicinal product. SAE was defined as any AE if it resulted in death or life-threatening AE or required inpatient hospitalization or prolongation of existing hospitalization or resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or was a congenital anomaly/birth defect. Safety analysis set included all subjects randomly assigned to treatment and who received at least 1 dose of study drug.

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

End point timeframe:

From date of first administration of study drug up to 28 days after last dose of study drug up to approximately 3 years 3 months

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: subjects | | | | |
| TEAE | 75 | 76 | | |
| SAE | 26 | 35 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Discontinuation due to an Adverse Event (AE)

| | |
|-----------------|--|
| End point title | Time to Treatment Discontinuation due to an Adverse Event (AE) |
|-----------------|--|

End point description:

Time to Treatment Discontinuation due to an AE (such as abdominal distention, appendicitis perforated, arthralgia, anemia, etc) was analyzed using the Kaplan-Meier method. Safety analysis set included all subjects randomly assigned to treatment and who received at least 1 dose of study drug. Here '99999' signifies that median and 95% CI were not estimable because insufficient number of subjects had events. As planned, data for this endpoint was analyzed and collected till Primary completion date.

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

End point timeframe:

From date of first administration of study drug up to approximately 2 years 6 months

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|----------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (84.3 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Dose Reductions

| | |
|-----------------|---------------------------|
| End point title | Number of Dose Reductions |
|-----------------|---------------------------|

End point description:

Number of dose reduction was reported as number of subjects who underwent one or more number of dose reductions. Safety analysis set included all subjects randomly assigned to treatment and who received at least 1 dose of study drug. As planned, data for this endpoint was analyzed and collected till Primary completion date.

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

End point timeframe:

From date of first administration of study drug up to approximately 2 years 6 months

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53 | 45 | | |
| Units: Subjects | | | | |
| 1 Dose Reduction | 17 | 20 | | |
| 2 Dose Reduction | 20 | 13 | | |
| 3 Dose Reduction | 13 | 8 | | |
| >=4 Dose Reduction | 3 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Dose Reduction

| | |
|---|------------------------------|
| End point title | Time to First Dose Reduction |
| End point description: Time to First Dose Reduction was analyzed using the Kaplan-Meier method. Safety analysis set included all subjects randomly assigned to treatment and who received at least 1 dose of study drug. As planned, data for this endpoint was analyzed and collected till Primary completion date. | |
| End point type | Secondary |
| End point timeframe: From date of first administration of study drug up to approximately 2 years 6 months | |

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 15.3 (12.1 to 20.1) | 24.1 (11.1 to 35.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Model Predicted Apparent Total Clearance (CL/F) Following Oral Dosing of Lenvatinib

| | |
|---|--|
| End point title | Model Predicted Apparent Total Clearance (CL/F) Following Oral Dosing of Lenvatinib ^[3] |
| End point description: Sparse pharmacokinetic (PK) samples (approximately 9 per subject) were collected and analyzed using | |

a population PK approach to estimate PK parameters. Lenvatinib total plasma concentration data were pooled with data from studies E7080-G000-303 (NCT01321554) and E7080-G000-201 (NCT00784303), and a population PK model was applied to the pooled dataset. Individual predicted CL/F for lenvatinib was then derived from the PK model by starting dose. PK Analysis Set included all subject who received at least one dose of study drug and who had evaluable lenvatinib plasma concentration data. Population for Lenvatinib 24 mg arm for this outcome measure included subject from study E7080-G000-303 (NCT01321554), E7080-G000-201 (NCT00784303) and from this current study E7080-G000-211. Here "overall number of subjects analyzed" signifies subjects who were evaluable for this outcome measure.

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

End point timeframe:

Cycle 1 Day 1:0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15:pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1:predose and 2-12 hours postdose (Cycle length=28 days)

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: Data were analyzed for the pooled Lenvatinib 24 mg arm only as planned.

| End point values | Lenvatinib 18 mg | Pooled Lenvatinib 24 mg | | |
|--------------------------------------|------------------|-------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 73 | 439 | | |
| Units: liter per hour (L/h) | | | | |
| arithmetic mean (standard deviation) | 6.243 (± 2.278) | 6.408 (± 1.945) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Model Predicted Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib

| | |
|-----------------|---|
| End point title | Model Predicted Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib ^[4] |
|-----------------|---|

End point description:

Sparse PK samples (approximately 9 per subject) were collected and analyzed using a population PK approach to estimate PK parameters. Lenvatinib total plasma concentration data were pooled with data from studies E7080-G000-303 (NCT01321554) and E7080-G000-201 (NCT00784303), and a population PK model was applied to the pooled dataset. Individual predicted CL/F for lenvatinib was then derived from the PK model by starting dose. PK Analysis Set included all subject who received at least one dose of study drug and who had evaluable lenvatinib plasma concentration data. Population for Lenvatinib 24 mg arm for this outcome measure included subject from study E7080-G000-303 (NCT01321554), E7080-G000-201 (NCT00784303) and from this current study E7080-G000-211. Here "overall number of subjects analyzed" signifies subjects who were evaluable for this outcome measure.

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

End point timeframe:

Cycle 1 Day 1:0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15:pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1:predose and 2-12 hours postdose (Cycle length=28 days)

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: Data were analyzed for the pooled Lenvatinib 24 mg arm only as planned

| End point values | Lenvatinib 18 mg | Pooled Lenvatinib 24 mg | | |
|---|------------------|-------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 73 | 439 | | |
| Units: nanogram*hour per milliliter (ng*h/mL) | | | | |
| arithmetic mean (standard deviation) | 3370 (± 4438) | 3747 (± 1295) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Parameter Estimates from the Population Pharmacokinetic/Pharmacodynamic (PK/PD) Model Describing the Relationship between Lenvatinib Exposure (AUC) and Thyroglobulin Levels

| | |
|-----------------|--|
| End point title | Parameter Estimates from the Population Pharmacokinetic/Pharmacodynamic (PK/PD) Model Describing the Relationship between Lenvatinib Exposure (AUC) and Thyroglobulin Levels |
|-----------------|--|

End point description:

The relationship between exposure to lenvatinib and change from baseline in thyroglobulin was planned to be analyzed using a model-based approach. PK/PD modeling of the effect of lenvatinib exposure on thyroglobulin levels could not be achieved due to the high variability in change from baseline data.

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

End point timeframe:

Cycle 1 Day 1:0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15:pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1:predose and 2-12 hours postdose (Cycle length=28 days)

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |

Notes:

[5] - Data was not collected and analyzed for this endpoint.

[6] - Data was not collected and analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Parameter Estimates from the Population Pharmacokinetic/Pharmacodynamic (PK/PD) Model Describing the Relationship between Lenvatinib Exposure (AUC) and Thyroid-Stimulating Hormone (TSH) Levels

| | |
|-----------------|--|
| End point title | Parameter Estimates from the Population Pharmacokinetic/Pharmacodynamic (PK/PD) Model Describing the Relationship between Lenvatinib Exposure (AUC) and Thyroid-Stimulating Hormone (TSH) Levels |
|-----------------|--|

End point description:

The relationship between exposure to lenvatinib and change from baseline in TSH was planned to be analyzed using a model-based approach. PK/PD modeling of the effect of lenvatinib exposure on TSH levels could not be achieved due to the high variability in change from baseline data.

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

End point timeframe:

Cycle 1 Day 1:0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15:pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1:predose and 2-12 hours postdose (Cycle length=28 days)

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |

Notes:

[7] - Data was not collected and analyzed for this endpoint.

[8] - Data was not collected and analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Level Estimates from the Population PK/PD Model Describing the Relationship between Lenvatinib Exposure (AUC) and Vascular Endothelial Growth Factor (VEGF), Soluble Tie-2, Angiopoietin-2 (Ang-2) and Fibroblast Growth Factor-23 (FGF23) Levels

| | |
|-----------------|--|
| End point title | Baseline Level Estimates from the Population PK/PD Model Describing the Relationship between Lenvatinib Exposure (AUC) and Vascular Endothelial Growth Factor (VEGF), Soluble Tie-2, Angiopoietin-2 (Ang-2) and Fibroblast Growth Factor-23 (FGF23) Levels |
|-----------------|--|

End point description:

Lenvatinib total plasma concentration and serum biomarkers of VEGF, Ang-2, soluble Tie-2, and FGF23 data were pooled with data from study E7080-G000-303 (NCT01321554) and the relationship between lenvatinib exposure at the time of measurement of biomarker was described using PK/PD modelling. Initially, PK/PD models were developed individually for each biomarker and then combined into a single combined model. Changes in biomarker levels over time related to lenvatinib exposure were best described by an indirect response, sigmoidal Emax model. For the final combined model, baseline level estimates were determined separately for each biomarker. PK/PD analysis was performed for DTC subject who received lenvatinib or placebo in study E7080-G000-303 (NCT01321554) and this current study E7080-G000-211 and provided both PK data for lenvatinib and baseline and post-dose serum biomarkers samples. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Cycle 1 Day 1:0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15:pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1:predose and 2-12 hours postdose (Cycle length=28 days)

| End point values | Pooled Lenvatinib or Placebo | | | |
|----------------------------------|------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 560 | | | |
| Units: nanogram per liter (ng/L) | | | | |
| number (confidence interval 95%) | | | | |
| VEGF(n=560) | 0.370 (0.355 to 0.385) | | | |
| Tie-2(n=560) | 14.6 (14.4 to 14.8) | | | |
| Ang-2(n=560) | 3.36 (3.26 to 3.46) | | | |
| FGF23(n=542) | 0.0990 (0.0949 to 0.103) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) Estimates from the Population PK/PD Model Describing the Relationship between Lenvatinib Exposure (AUC) and VEGF, Soluble Tie-2, Ang-2 and FGF23 Levels

| | |
|-----------------|---|
| End point title | Mean Residence Time (MRT) Estimates from the Population PK/PD Model Describing the Relationship between Lenvatinib Exposure (AUC) and VEGF, Soluble Tie-2, Ang-2 and FGF23 Levels |
|-----------------|---|

End point description:

Lenvatinib total plasma concentration and serum biomarkers of VEGF, Ang-2, soluble Tie-2, and FGF23 data were pooled with data from study E7080-G000-303 (NCT01321554) and the relationship between lenvatinib exposure at the time of measurement of biomarker was described using PK/PD modelling. Initially, PK/PD models were developed individually for each biomarker and then combined into a single combined model. Changes in biomarker levels over time related to lenvatinib exposure were best described by an indirect response, sigmoidal Emax model. For the final combined model, MRT estimates were determined separately for each biomarker. PK/PD analysis was performed for DTC subjects who received lenvatinib or placebo in study E7080-G000-303 (NCT01321554) and this current study E7080-G000-211 and provided both PK data for lenvatinib and baseline and post-dose serum biomarkers samples. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1: predose and 2-12 hours postdose (Cycle length=28 days)

| End point values | Pooled Lenvatinib or Placebo | | | |
|----------------------------------|------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 560 | | | |
| Units: hours | | | | |
| number (confidence interval 95%) | | | | |
| VEGF(n=560) | 58.3 (23.4 to 93.2) | | | |

| | | | | |
|--------------|------------------|--|--|--|
| Tie-2(n=560) | 354 (314 to 394) | | | |
| Ang-2(n=560) | 173 (134 to 212) | | | |
| FGF23(n=542) | 265 (185 to 345) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hill Coefficient Estimates from the Population PK/PD Model Describing the Relationship between Lenvatinib Exposure (AUC) and VEGF, Soluble Tie-2, Ang-2 and FGF23 Levels

| | |
|-----------------|--|
| End point title | Hill Coefficient Estimates from the Population PK/PD Model Describing the Relationship between Lenvatinib Exposure (AUC) and VEGF, Soluble Tie-2, Ang-2 and FGF23 Levels |
|-----------------|--|

End point description:

Lenvatinib total plasma concentration and serum biomarkers of VEGF, Ang-2, soluble Tie-2, and FGF23 data were pooled with data from study E7080-G000-303 (NCT01321554) and the relationship between lenvatinib exposure at the time of measurement of biomarker was described using PK/PD modelling. Initially, PK/PD models were developed individually for each biomarker and then combined into a single combined model. Changes in biomarker levels over time related to lenvatinib exposure were best described by an indirect response, sigmoidal Emax model. For the final combined model, Hill Coefficient estimates were determined separately for each biomarker. PK/PD analysis was performed for DTC subjects who received lenvatinib or placebo in study E7080-G000-303 (NCT01321554) and this current study E7080-G000-211 and provided both PK data for lenvatinib and baseline and post-dose serum biomarkers samples. Here '99999' signifies upper and lower 95% CI was not estimable as Hill coefficient was fixed to 1.

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

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 8: predose, Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 22: optionally at predose; Cycle 2 Day 1: predose and 2-12 hours postdose (Cycle length=28 days)

| End point values | Pooled Lenvatinib or Placebo | | | |
|----------------------------------|------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 560 ^[9] | | | |
| Units: unitless | | | | |
| number (confidence interval 95%) | | | | |
| VEGF(n=560) | 1.00 (-99999 to 99999) | | | |
| Tie-2(n=560) | 0.313 (0.242 to 0.384) | | | |
| Ang-2(n=560) | 4.27 (2.92 to 5.62) | | | |
| FGF23(n=542) | 1.0 (-99999 to 99999) | | | |

Notes:

[9] - N=overall subject analyzed; n=subjects analyzed for given categories.

Statistical analyses

No statistical analyses for this end point

Secondary: Parameter Estimates from the PK/PD Model for Tumor Growth Inhibition and Serum Biomarkers Tie-2 and Ang-2

| | |
|-----------------|---|
| End point title | Parameter Estimates from the PK/PD Model for Tumor Growth Inhibition and Serum Biomarkers Tie-2 and Ang-2 |
|-----------------|---|

End point description:

Tumor-growth inhibition models were based on placebo and lenvatinib data from the current study E7080-G000-211 and E7080-G000-303(NCT01321554), where the effects of tumor growth rate, drug effects, tumor resistance, and tumor size reduction related to biomarker response were assessed. Longitudinal data of the sum of the longest diameter for target lesion by investigator assessment in this study and independent reviewer assessment in study E7080-G000-303 was used. Changes in Ang-2 and soluble Tie-2 were evaluated, individually and in combination for their impact on tumor size. The final integrated model for tumor growth/biomarkers included the effects of lenvatinib exposure and tumor growth reduction related to Tie-2 and Ang-2 biomarkers as significant predictors. PK/PD analysis of tumor size was performed for DTC subjects in study E7080-G000-303 (NCT01321554) and the current study E7080-G000-211 who had PK data and at least one post-baseline tumor evaluation. N=overall subject analyzed.

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

End point timeframe:

Baseline up to week 120

| End point values | Pooled Lenvatinib or Placebo | | | |
|----------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 558 | | | |
| Units: per week | | | | |
| number (confidence interval 95%) | | | | |
| Tumor growth rate | 0.00249 (0.00177 to 0.00321) | | | |
| Emax | 0.0877 (0.0843 to 0.0911) | | | |
| Resistance term | 0.268 (0.253 to 0.283) | | | |
| constant for Tie-2 | -0.0220 (-0.0247 to 0.0193) | | | |
| constant for Ang-2 | -0.0146 (-0.0158 to -0.0134) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenvatinib Mean AUC Resulting in 50% of the Emax (EC50) Estimate from the PK/PD Model for Tumor Growth Inhibition and Serum Biomarkers Tie-2 and Ang-2

| | |
|---|--|
| End point title | Lenvatinib Mean AUC Resulting in 50% of the Emax (EC50) Estimate from the PK/PD Model for Tumor Growth Inhibition and Serum Biomarkers Tie-2 and Ang-2 |
| End point description: | |
| Tumor growth inhibition models were based on placebo and lenvatinib data from the current study E7080-G000-211 and E7080-G000-303(NCT01321554), where the effects of tumor growth rate, drug effects, tumor resistance, and tumor size reduction related to biomarker response were assessed. Longitudinal data of the sum of the longest diameter for target lesion by investigator assessment in this study and independent reviewer assessment in study E7080-G000-303 was used. Changes in Ang-2 and soluble Tie-2 were evaluated individually and in combination for their impact on tumor size. The final integrated model for tumor growth and biomarkers included the effects of lenvatinib exposure and tumor growth reduction related to Tie-2 and Ang-2 biomarkers as significant predictors. PK/PD analysis of tumor size was performed for DTC subjects in study E7080-G000-303(NCT01321554) and the current study E7080-G000-211 who had PK data and at least one post-baseline tumor evaluation. N=overall subject analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to week 120 | |

| End point values | Pooled Lenvatinib or Placebo | | | |
|----------------------------------|------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 558 | | | |
| Units: ng*h/mL | | | | |
| number (confidence interval 95%) | 1760 (1490 to 2030) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Scale Factor Estimate for Final Parametric Time to Event PK/PD Model for PFS

| | |
|--|--|
| End point title | Scale Factor Estimate for Final Parametric Time to Event PK/PD Model for PFS |
| End point description: | |
| PK/PD analysis for PFS was based on data from current study E7080-G000-211, E7080-G000-303 (NCT01321554). Direct relationship between lenvatinib exposure and PFS were assessed using Kaplan-Meier plots stratified by quartile and median lenvatinib exposure. A parametric survival model (proportional hazard model) with Weibull distribution structure was developed to estimate the probability distribution of the time from study start to subject progression, as a function of various covariates (predictors) including baseline disease characteristics, demographics, lenvatinib exposure, changes in biomarkers time profiles, model predicted change from baseline in tumor size and change in tumor size time-profiles. Significant ($p < 0.01$) independent predictors from the univariate analysis were added to the model simultaneously and significant predictors were kept in the model according to backward exclusion criteria (log likelihood ratio test, p -value of 0.001). N=overall subject analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first up to approximately 3 years 3 months | |

| End point values | Pooled Lenvatinib or Placebo: PFS | | | |
|----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 475 ^[10] | | | |
| Units: per week | | | | |
| number (confidence interval 95%) | | | | |
| Scale factor | 0.00700 (0.00353 to 0.0105) | | | |
| Scale factor drop out | 99999 (99999 to 99999) | | | |

Notes:

[10] - Number for Scale factor drop out is 0.0000935, upper and lower 95% CI is 0.000000188 and 0.000187

Statistical analyses

No statistical analyses for this end point

Secondary: Shape Factor Estimate for Final Parametric Time to Event PK/PD Model for PFS

| | |
|-----------------|--|
| End point title | Shape Factor Estimate for Final Parametric Time to Event PK/PD Model for PFS |
|-----------------|--|

End point description:

PK/PD analysis for PFS was based on data from current study E7080-G000-211, E7080-G000-303 (NCT01321554). Direct relationship between lenvatinib exposure and PFS were assessed using Kaplan-Meier plots stratified by quartile and median lenvatinib exposure. A parametric survival model (proportional hazard model) with Weibull distribution structure was developed to estimate the probability distribution of the time from study start to subject progression, as a function of various covariates (predictors) including baseline disease characteristics, demographics, lenvatinib exposure, changes in biomarkers time profiles, model predicted change from baseline in tumor size and change in tumor size time-profiles. Significant ($p < 0.01$) independent predictors from the univariate analysis were added to the model simultaneously and significant predictors were kept in the model according to backward exclusion criteria (log likelihood ratio test, p -value of 0.001). N =overall subject analyzed.

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

End point timeframe:

Time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first up to approximately 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: PFS | | | |
|----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 475 | | | |
| Units: Unitless | | | | |
| number (confidence interval 95%) | | | | |
| Shape factor | 1.36 (1.22 to 1.50) | | | |
| Shape factor drop out | 2.19 (1.96 to 2.42) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenvatinib AUC Exposure Effect Estimate for Final Parametric Time to Event PK/PD Model for PFS

| | |
|-----------------|--|
| End point title | Lenvatinib AUC Exposure Effect Estimate for Final Parametric Time to Event PK/PD Model for PFS |
|-----------------|--|

End point description:

PK/PD analysis for PFS was based on data from current study E7080-G000-211, E7080-G000-303 (NCT01321554). Direct relationship between lenvatinib exposure and PFS were assessed using Kaplan-Meier plots stratified by quartile and median lenvatinib exposure. A parametric survival model (proportional hazard model) with Weibull distribution structure was developed to estimate the probability distribution of the time from study start to subject progression, as a function of various covariates (predictors) including baseline disease characteristics, demographics, lenvatinib exposure, changes in biomarkers time profiles, model predicted change from baseline in tumor size and change in tumor size time-profiles. Significant ($p < 0.01$) independent predictors from the univariate analysis were added to the model simultaneously and significant predictors were kept in the model according to backward exclusion criteria (log likelihood ratio test, p -value of 0.001). N =overall subject analyzed.

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

End point timeframe:

Time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first up to approximately 3 years 3 months

| | | | | |
|--|-----------------------------------|--|--|--|
| End point values | Pooled Lenvatinib or Placebo: PFS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 475 | | | |
| Units: per microgram*week per milliliter | | | | |
| number (confidence interval 95%) | 0.00111 (0.000542 to 0.00168) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Predicted Percent Change in Tumor Size Estimate for Final Parametric Time to Event PK/PD Model for PFS

| | |
|-----------------|--|
| End point title | Predicted Percent Change in Tumor Size Estimate for Final Parametric Time to Event PK/PD Model for PFS |
|-----------------|--|

End point description:

PK/PD analysis for PFS was based on data from current study E7080-G000-211, E7080-G000-303 (NCT01321554). Direct relationship between lenvatinib exposure and PFS were assessed using Kaplan-

Meier plots stratified by quartile and median lenvatinib exposure. A parametric survival model (proportional hazard model) with Weibull distribution structure was developed to estimate the probability distribution of the time from study start to subject progression, as a function of various covariates (predictors) including baseline disease characteristics, demographics, lenvatinib exposure, changes in biomarkers time profiles, model predicted change from baseline in tumor size and change in tumor size time-profiles. Significant ($p < 0.01$) independent predictors from the univariate analysis were added to the model simultaneously and significant predictors were kept in the model according to backward exclusion criteria (log likelihood ratio test, p-value of 0.001). N=overall subject analyzed.

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

End point timeframe:

Time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first up to approximately 3 years 3 months

| | | | | |
|----------------------------------|-----------------------------------|--|--|--|
| End point values | Pooled Lenvatinib or Placebo: PFS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 475 | | | |
| Units: Percent change | | | | |
| number (confidence interval 95%) | -0.0523 (-0.0629 to -0.0417) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Tumor Size Estimate for Final Parametric Time to Event PK/PD Model for PFS

| | |
|-----------------|---|
| End point title | Baseline Tumor Size Estimate for Final Parametric Time to Event PK/PD Model for PFS |
|-----------------|---|

End point description:

PK/PD analysis for PFS was based on data from current study E7080-G000-211, E7080-G000-303 (NCT01321554). Direct relationship between lenvatinib exposure and PFS were assessed using Kaplan-Meier plots stratified by quartile and median lenvatinib exposure. A parametric survival model (proportional hazard model) with Weibull distribution structure was developed to estimate the probability distribution of the time from study start to subject progression, as a function of various covariates (predictors) including baseline disease characteristics, demographics, lenvatinib exposure, changes in biomarkers time profiles, model predicted change from baseline in tumor size and change in tumor size time-profiles. Significant ($p < 0.01$) independent predictors from the univariate analysis were added to the model simultaneously and significant predictors were kept in the model according to backward exclusion criteria (log likelihood ratio test, p-value of 0.001). N=overall subject analyzed.

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

End point timeframe:

Time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurs first up to approximately 3 years 3 months

| | | | | |
|----------------------------------|-----------------------------------|--|--|--|
| End point values | Pooled Lenvatinib or Placebo: PFS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 475 | | | |
| Units: per millimeter (/mm) | | | | |
| number (confidence interval 95%) | -0.00547 (-0.00821 to -0.00273) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Input Rate Indirect Effect Model Estimate from Base/Final PK/PD Blood Pressure Model

| | |
|-----------------|--|
| End point title | Input Rate Indirect Effect Model Estimate from Base/Final PK/PD Blood Pressure Model |
|-----------------|--|

End point description:

PK/PD analysis for blood pressure was based on pooled data from current study E7080-G000-211, study E7080-G000-201 (NCT00784303) and study E7080-G000-303 (NCT01321554). The effect of lenvatinib exposure (AUC) at the time of blood pressure assessment on systolic and diastolic blood pressure was tested as a simultaneous indirect model where lenvatinib AUC was linked to the input rate of the indirect effect model by a linear slope factor function. Based on the results from model development an indirect PK/PD model with a linear effect of lenvatinib exposure on both systolic and diastolic blood pressure was selected as the base model for subsequent univariate analysis. For PK/PD analyses of blood pressure, subjects receiving lenvatinib in studies E7080-G000-211, E7080-G000-201 (NCT00784303) and E7080-G000-303 (NCT01321554), with PK information and who had at least one post-baseline evaluation, and subjects receiving placebo in study E7080-G000-303 were included. N=overall subject analyzed.

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

End point timeframe:

From date of first administration of study drug up to 6 months

| | | | | |
|--|--------------------------------------|--|--|--|
| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 660 | | | |
| Units: millimeters of mercury per hour | | | | |
| number (confidence interval 95%) | 2.76 (0.978 to 4.54) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Drug Effect on Systolic and Diastolic Input Rate Estimates from Base/Final PK/PD Blood Pressure Model

| | |
|-----------------|---|
| End point title | Drug Effect on Systolic and Diastolic Input Rate Estimates from |
|-----------------|---|

End point description:

PK/PD analysis for blood pressure was based on pooled data from current study E7080-G000-211, study E7080-G000-201 (NCT00784303) and study E7080-G000-303 (NCT01321554). The effect of lenvatinib exposure (AUC) at the time of blood pressure assessment on systolic and diastolic blood pressure was tested as a simultaneous indirect model where lenvatinib AUC was linked to the input rate of the indirect effect model by a linear slope factor function. Based on the results from model development an indirect PK/PD model with a linear effect of lenvatinib exposure on both systolic and diastolic blood pressure was selected as the base model for subsequent univariate analysis. For PK/PD analyses of blood pressure, subjects receiving lenvatinib in studies E7080-G000-211, E7080-G000-201 (NCT00784303) and E7080-G000-303 (NCT01321554), with PK information and who had at least one post-baseline evaluation, and subjects receiving placebo in study E7080-G000-303 were included. N=overall subject analyzed.

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

End point timeframe:

From date of first administration of study drug up to 6 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|---|--------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 660 | | | |
| Units: per nanogram*hour per mL*10 ⁶ | | | | |
| number (confidence interval 95%) | | | | |
| Drug effect on systolic input rate | 12.0 (10.8 to 13.2) | | | |
| Drug effect on diastolic input rate | 21.1 (19.0 to 23.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Weight Decrease Stratified by AUC Quartile (Q) Group

| | |
|-----------------|--|
| End point title | Number of Subjects With Weight Decrease Stratified by AUC Quartile (Q) Group |
|-----------------|--|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE weight decreased was based on pooled data from current study E7080-G000-211, study E7080-G000-201 (NCT00784303) and study E7080-G000-303 (NCT01321554). Relationship of occurrence probability of different grades of TEAE weight decreased and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1 (mild), 2 (moderate) or 3 (severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 82 | | | |
| AUC Q1; Grade 1(N=135) | 20 | | | |
| AUC Q1; Grade 2(N=135) | 29 | | | |
| AUC Q1; Grade 3(N=135) | 4 | | | |
| AUC Q2; None(N=135) | 75 | | | |
| AUC Q2; Grade 1(N=135) | 17 | | | |
| AUC Q2; Grade 2(N=135) | 28 | | | |
| AUC Q2; Grade 3(N=135) | 15 | | | |
| AUC Q3; None(N=135) | 74 | | | |
| AUC Q3; Grade 1(N=136) | 18 | | | |
| AUC Q3; Grade 2(N=136) | 33 | | | |
| AUC Q3; Grade 3(N=136) | 11 | | | |
| AUC Q4; None(N=135) | 67 | | | |
| AUC Q4; Grade 1(N=135) | 15 | | | |
| AUC Q4; Grade 2(N=135) | 37 | | | |
| AUC Q4; Grade 3(N=135) | 16 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hypertension Stratified by AUC Quartile (Q) Group

| | |
|-----------------|---|
| End point title | Number of Subjects With Hypertension Stratified by AUC Quartile (Q) Group |
|-----------------|---|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE hypertension was based on pooled data from current study E7080-G000-211, study E7080-G000-201(NCT00784303) and study E7080-G000-303(NCT01321554). Relationship of occurrence probability of different grades of TEAE hypertension and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1(mild), 2(moderate), or 3/4 (severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 54 | | | |
| AUC Q1; Grade 1(N=135) | 14 | | | |
| AUC Q1; Grade 2(N=135) | 37 | | | |
| AUC Q1; Grade 3(N=135) | 30 | | | |
| AUC Q1; Grade 4(N=135) | 0 | | | |
| AUC Q2; None(N=135) | 48 | | | |
| AUC Q2; Grade 1(N=135) | 11 | | | |
| AUC Q2; Grade 2(N=135) | 30 | | | |
| AUC Q2; Grade 3(N=135) | 47 | | | |
| AUC Q2; Grade 4(N=135) | 0 | | | |
| AUC Q3; None(N=136) | 45 | | | |
| AUC Q3; Grade 1(N=136) | 10 | | | |
| AUC Q3; Grade 2(N=136) | 31 | | | |
| AUC Q3; Grade 3(N=136) | 50 | | | |
| AUC Q3; Grade 4(N=136) | 0 | | | |
| AUC Q4; None(N=135) | 51 | | | |
| AUC Q4; Grade 1(N=135) | 12 | | | |
| AUC Q4; Grade 2(N=135) | 31 | | | |
| AUC Q4; Grade 3(N=135) | 40 | | | |
| AUC Q4; Grade 4(N=135) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Proteinuria Stratified by AUC Quartile (Q) Group

| | |
|-----------------|--|
| End point title | Number of Subjects With Proteinuria Stratified by AUC Quartile (Q) Group |
|-----------------|--|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE proteinuria was based on pooled data from current study E7080-G000-211, study E7080-G000-201 (NCT00784303) and study E7080-G000-303 (NCT01321554). Relationship of occurrence probability of different grades of TEAE proteinuria and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1 (mild), 2 (moderate), or 3 (severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:
Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 104 | | | |
| AUC Q1; Grade 1(N=135) | 12 | | | |
| AUC Q1; Grade 2(N=135) | 13 | | | |
| AUC Q1; Grade 3(N=135) | 6 | | | |
| AUC Q2; None(N=135) | 92 | | | |
| AUC Q2; Grade 1(N=135) | 7 | | | |
| AUC Q2; Grade 2(N=135) | 21 | | | |
| AUC Q2; Grade 3(N=135) | 15 | | | |
| AUC Q3; None(N=136) | 72 | | | |
| AUC Q3; Grade 1(N=136) | 16 | | | |
| AUC Q3; Grade 2(N=136) | 32 | | | |
| AUC Q3; Grade 3(N=136) | 16 | | | |
| AUC Q4; None(N=135) | 72 | | | |
| AUC Q4; Grade 1(N=135) | 19 | | | |
| AUC Q4; Grade 2(N=135) | 34 | | | |
| AUC Q4; Grade 3(N=135) | 10 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Fatigue Stratified by AUC Quartile (Q) Group

| | |
|-----------------|--|
| End point title | Number of Subjects With Fatigue Stratified by AUC Quartile (Q) Group |
|-----------------|--|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE fatigue was based on pooled data from current study E7080-G000-211, study E7080-G000-201(NCT00784303) and study E7080-G000-303(NCT01321554). Relationship of occurrence probability of different grades of TEAE fatigue and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1(mild), 2(moderate), or 3(severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 75 | | | |
| AUC Q1; Grade 1(N=135) | 27 | | | |
| AUC Q1; Grade 2(N=135) | 30 | | | |
| AUC Q1; Grade 3(N=135) | 3 | | | |
| AUC Q2; None(N=135) | 81 | | | |
| AUC Q2; Grade 1(N=135) | 32 | | | |
| AUC Q2; Grade 2(N=135) | 17 | | | |
| AUC Q2; Grade 3(N=135) | 5 | | | |
| AUC Q3; None(N=136) | 73 | | | |
| AUC Q3; Grade 1(N=136) | 42 | | | |
| AUC Q3; Grade 2(N=136) | 11 | | | |
| AUC Q3; Grade 3(N=136) | 10 | | | |
| AUC Q4;None(N=135) | 79 | | | |
| AUC Q4;Grade 1(N=135) | 25 | | | |
| AUC Q4;Grade 2(N=135) | 26 | | | |
| AUC Q4;Grade 3(N=135) | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Diarrhea Stratified by AUC Quartile (Q) Group

| | |
|-----------------|---|
| End point title | Number of Subjects With Diarrhea Stratified by AUC Quartile (Q) Group |
|-----------------|---|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE diarrhea was based on pooled data from current study E7080-G000-211, study E7080-G000-201 (NCT00784303) and study E7080-G000-303 (NCT01321554). Relationship of occurrence probability of different grades of TEAE diarrhea and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1 (mild), 2 (moderate), or 3 (severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 55 | | | |
| AUC Q1; Grade 1(N=135) | 39 | | | |
| AUC Q1; Grade 2(N=135) | 35 | | | |
| AUC Q1; Grade 3(N=135) | 6 | | | |
| AUC Q2; None(N=135) | 53 | | | |
| AUC Q2; Grade 1(N=135) | 45 | | | |
| AUC Q2; Grade 2(N=135) | 29 | | | |
| AUC Q2; Grade 3(N=135) | 8 | | | |
| AUC Q3; None(N=136) | 52 | | | |
| AUC Q3; Grade 1(N=136) | 34 | | | |
| AUC Q3; Grade 2(N=136) | 33 | | | |
| AUC Q3; Grade 3(N=136) | 17 | | | |
| AUC Q4; None(N=135) | 56 | | | |
| AUC Q4; Grade 1(N=135) | 37 | | | |
| AUC Q4; Grade 2(N=135) | 34 | | | |
| AUC Q4; Grade 3(N=135) | 8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Nausea Stratified by AUC Quartile (Q) Group

| | |
|-----------------|---|
| End point title | Number of Subjects With Nausea Stratified by AUC Quartile (Q) Group |
|-----------------|---|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE nausea was based on pooled data from current study E7080-G000-211, study E7080-G000-201(NCT00784303) and study E7080-G000-303(NCT01321554). Relationship of occurrence probability of different grades of TEAE nausea and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1(mild), 2(moderate), or 3(severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 88 | | | |
| AUC Q1; Grade 1(N=135) | 32 | | | |
| AUC Q1; Grade 2(N=135) | 14 | | | |
| AUC Q1; Grade 3(N=135) | 1 | | | |
| AUC Q2; None(N=135) | 79 | | | |
| AUC Q2; Grade 1(N=135) | 36 | | | |
| AUC Q2; Grade 2(N=135) | 18 | | | |
| AUC Q2; Grade 3(N=135) | 2 | | | |
| AUC Q3; None(N=136) | 83 | | | |
| AUC Q3; Grade 1(N=136) | 37 | | | |
| AUC Q3; Grade 2(N=136) | 14 | | | |
| AUC Q3; Grade 3(N=136) | 2 | | | |
| AUC Q4; None(N=135) | 63 | | | |
| AUC Q4; Grade 1(N=135) | 41 | | | |
| AUC Q4; Grade 2(N=135) | 29 | | | |
| AUC Q4; Grade 3(N=135) | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Vomiting Stratified by AUC Quartile (Q) Group

| | |
|-----------------|---|
| End point title | Number of Subjects With Vomiting Stratified by AUC Quartile (Q) Group |
|-----------------|---|

End point description:

PK/PD analysis of the relationship between lenvatinib exposure and occurrence of TEAE vomiting was based on pooled data from current study E7080-G000-211, study E7080-G000-201(NCT00784303) and study E7080-G000-303(NCT01321554). Relationship of occurrence probability of different grades of TEAE vomiting and lenvatinib exposure was evaluated by logistic regression model. Logit model was of the form: sum of intercept, of lenvatinib exposure, effects of covariates was explored, random effects was used to describe between subject variability. Lenvatinib exposure was AUC based on the dose at time of event. For each TEAE, probabilities of having no TEAE and CTCAE grade 1(mild), 2(moderate), or 3(severe) TEAE was estimated as function of lenvatinib exposure. For PK/PD analysis, subjects with DTC from studies E7080-G000-211, E7080-G000-201, E7080-G000-303 with PK data, who had at least 1 postbaseline evaluation was included. N=overall subject analyzed; n=subjects analyzed for given categories.

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

End point timeframe:

Up to 3 years 3 months

| End point values | Pooled Lenvatinib or Placebo: Safety | | | |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 136 | | | |
| Units: Subjects | | | | |
| AUC Q1; None(N=135) | 106 | | | |
| AUC Q1; Grade 1(N=135) | 19 | | | |
| AUC Q1; Grade 2(N=135) | 7 | | | |
| AUC Q1; Grade 3(N=135) | 3 | | | |
| AUC Q2; None(N=135) | 100 | | | |
| AUC Q2; Grade 1(N=135) | 21 | | | |
| AUC Q2; Grade 2(N=135) | 11 | | | |
| AUC Q2; Grade 3(N=135) | 3 | | | |
| AUC Q3; None(N=136) | 94 | | | |
| AUC Q3; Grade 1(N=136) | 31 | | | |
| AUC Q3; Grade 2(N=136) | 8 | | | |
| AUC Q3; Grade 3(N=136) | 3 | | | |
| AUC Q4; None(N=135) | 86 | | | |
| AUC Q4; Grade 1(N=135) | 30 | | | |
| AUC Q4; Grade 2(N=135) | 18 | | | |
| AUC Q4; Grade 3(N=135) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Health-Related Quality of Life (HRQoL) Assessed by European Quality of Life (EuroQol) Five-Dimensional, 3-Level (EQ-5D-3L) Index Score and Visual Analogue Scale (VAS)

| | |
|-----------------|--|
| End point title | Change From Baseline in the Health-Related Quality of Life (HRQoL) Assessed by European Quality of Life (EuroQol) Five-Dimensional, 3-Level (EQ-5D-3L) Index Score and Visual Analogue Scale (VAS) |
|-----------------|--|

End point description:

The EQ-5D-3L is a health profile questionnaire assessing quality of life along 5 dimensions. Subjects rate 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). The summed score ranges from 5-15 with "5" corresponding to no problems and "15" corresponding to severe problems in the 5 dimensions. EQ-5D-3L also included an EQ visual analogue scale (VAS) that ranges between 100 (best imaginable health) and 0 (worst imaginable health). Decrease from baseline in EQ-5D-3L signifies improvement. Total index EQ-5D-3L summary score was weighted with a range of -0.594 (worst) to 1.0 (best). EQ-5D-3L also included an EQ health utilities index (HUI) where 1 indicated full health while a score of 0 indicated worst health/death. FAS included all subjects randomly assigned to treatment.

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

End point timeframe:

Baseline, Week 8, 16, and 24

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| EQ HUI; Baseline | 0.8 (± 0.17) | 0.8 (± 0.23) | | |
| EQ-HUI; Change at week 8 | -0.1 (± 0.19) | 0.0 (± 0.15) | | |
| EQ-HUI; Change at week 16 | -0.1 (± 0.20) | -0.1 (± 0.22) | | |
| EQ-HUI; Change at week 24 | -0.1 (± 0.17) | 0.1 (± 0.19) | | |
| EQ-VAS; Baseline | 71.1 (± 19.12) | 69.2 (± 21.29) | | |
| EQ-VAS; Change at week 8 | -6.2 (± 15.71) | -1.4 (± 19.46) | | |
| EQ-VAS; Change at week 16 | -6.3 (± 17.08) | -9.8 (± 17.82) | | |
| EQ-VAS; Change at week 24 | -3.1 (± 12.95) | -5.1 (± 23.41) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the HRQoL Assessed by Functional Assessment of Cancer Therapy-General (FACT-G) Total Score

| | |
|-----------------|--|
| End point title | Change From Baseline in the HRQoL Assessed by Functional Assessment of Cancer Therapy-General (FACT-G) Total Score |
|-----------------|--|

End point description:

The FACT-G is a 27-item questionnaire that measures the effect of cancer treatment on quality of life that has four areas of measurements (physical well-being, social/family well-being, emotional well-being and functional well-being). Each item has a 5-point scale response set (0: not at all; 1: a little bit; 2: somewhat; 3: quite a bit; and 4: very much). The FACT-G total score ranges between 0 and 108. Higher score indicates better quality of life. FAS included all subjects randomly assigned to treatment.

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

End point timeframe:

Baseline, Week 8, 16 and 24

| End point values | Lenvatinib 24 mg | Lenvatinib 18 mg | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 77 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| At Baseline | 81.1 (± 16.18) | 77.8 (± 16.04) | | |
| Change at Week 8 | -3.0 (± 12.26) | -1.3 (± 13.31) | | |
| Change at Week 16 | -4.5 (± 12.64) | -3.8 (± 14.75) | | |
| Change at Week 24 | -6.3 (± 15.49) | -1.5 (± 16.74) | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first administration of study drug up to 28 days after last dose of study drug up to approximately 3 years 3 months

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Lenvatinib 18 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subject received a total of 4 capsules in the form of one 10-mg capsule and two 4-mg capsules containing lenvatinib and one 10-mg placebo capsule.

| | |
|-----------------------|------------------|
| Reporting group title | Lenvatinib 24 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received lenvatinib 24 mg, capsule, orally, once daily in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first (up to 35 months). To maintain blinded treatment assignment, subject received a total of 4 capsules in the form of two 10-mg capsules and one 4-mg capsule containing lenvatinib and one 4-mg placebo capsule.

| Serious adverse events | Lenvatinib 18 mg | Lenvatinib 24 mg | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 77 (45.45%) | 26 / 75 (34.67%) | |
| number of deaths (all causes) | 19 | 11 | |
| number of deaths resulting from adverse events | 3 | 6 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Malignant pleural effusion | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastases to spine | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|---|----------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumomediastinum | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Mental status changes | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Post procedural complication subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subdural haematoma subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous haematoma subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuropericarditis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post-traumatic epilepsy | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal vascular occlusion | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Proteinuria | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint ankylosis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Lenvatinib 18 mg | Lenvatinib 24 mg | |
|---|------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 77 (98.70%) | 75 / 75 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Cancer pain | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 0 / 75 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 0 / 75 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Tumour haemorrhage | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Tumour necrosis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin cancer | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Flushing | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 40 / 77 (51.95%) | 44 / 75 (58.67%) | |
| occurrences (all) | 91 | 127 | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 2 / 75 (2.67%) | |
| occurrences (all) | 7 | 3 | |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|------------------------|------------------------|--|
| Vasculitis subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 21 / 77 (27.27%) 51 | 18 / 75 (24.00%) 34 | |
| Axillary pain subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Catheter site pain subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Chest discomfort subjects affected / exposed occurrences (all) | 3 / 77 (3.90%) 3 | 1 / 75 (1.33%) 1 | |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Chills subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 3 / 75 (4.00%) 5 | |
| Discomfort subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Early satiety subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Face oedema subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 | 0 / 75 (0.00%) 0 | |
| Facial pain | | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) |
| occurrences (all) | 3 | 1 |
| Feeling abnormal | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Fatigue | | |
| subjects affected / exposed | 28 / 77 (36.36%) | 30 / 75 (40.00%) |
| occurrences (all) | 56 | 60 |
| Gait disturbance | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Generalised oedema | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 3 | 3 |
| Hyperthermia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Impaired healing | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 2 |
| Induration | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Influenza like illness | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 4 / 75 (5.33%) |
| occurrences (all) | 3 | 5 |
| Non-cardiac chest pain | | |
| subjects affected / exposed | 8 / 77 (10.39%) | 3 / 75 (4.00%) |
| occurrences (all) | 11 | 3 |
| Malaise | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Oedema | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Oedema peripheral | | |

| | | | |
|---|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 12 / 77 (15.58%) 19 | 16 / 75 (21.33%) 25 | |
| Pain subjects affected / exposed occurrences (all) | 4 / 77 (5.19%) 6 | 3 / 75 (4.00%) 3 | |
| Pyrexia subjects affected / exposed occurrences (all) | 7 / 77 (9.09%) 9 | 4 / 75 (5.33%) 4 | |
| Temperature intolerance subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 75 (2.67%) 2 | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 1 / 75 (1.33%) 1 | |
| Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Breast pain subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Erectile dysfunction subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Genital haemorrhage subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Ovarian cyst subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Menstruation irregular subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Pelvic pain | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Varicocele | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Increased upper airway secretion | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cough | | | |
| subjects affected / exposed | 19 / 77 (24.68%) | 10 / 75 (13.33%) | |
| occurrences (all) | 24 | 10 | |
| Dysphonia | | | |
| subjects affected / exposed | 20 / 77 (25.97%) | 16 / 75 (21.33%) | |
| occurrences (all) | 26 | 18 | |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 77 (16.88%) | 12 / 75 (16.00%) | |
| occurrences (all) | 16 | 15 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 1 / 75 (1.33%) | |
| occurrences (all) | 4 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 7 / 77 (9.09%) | 4 / 75 (5.33%) | |
| occurrences (all) | 15 | 5 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoxia | | | |

| | | |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hiccups | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nasal congestion | | |
| subjects affected / exposed | 7 / 77 (9.09%) | 5 / 75 (6.67%) |
| occurrences (all) | 7 | 5 |
| Nasal dryness | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Oropharyngeal pain | | |
| subjects affected / exposed | 8 / 77 (10.39%) | 4 / 75 (5.33%) |
| occurrences (all) | 9 | 4 |
| Orthopnoea | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 2 |
| Pharyngeal swelling | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pharyngeal inflammation | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Pleural effusion | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 1 / 75 (1.33%) |
| occurrences (all) | 3 | 1 |
| Pleuritic pain | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Pneumonitis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Respiratory disorder | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Pulmonary embolism | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 3 / 75 (4.00%) | |
| occurrences (all) | 1 | 3 | |
| Productive cough | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 2 / 75 (2.67%) | |
| occurrences (all) | 4 | 2 | |
| Rhinalgia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) | |
| occurrences (all) | 1 | 4 | |
| Sinus congestion | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus pain | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Sputum increased | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 1 / 75 (1.33%) | |
| occurrences (all) | 3 | 1 | |
| Throat irritation | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|------------------------------------|-----------------|------------------|--|
| Anxiety | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 6 / 75 (8.00%) | |
| occurrences (all) | 2 | 6 | |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Depression | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 7 / 75 (9.33%) | |
| occurrences (all) | 4 | 7 | |
| Insomnia | | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 6 / 75 (8.00%) | |
| occurrences (all) | 8 | 7 | |
| Hallucination | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Libido decreased | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Irritability | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| Nervousness | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thermophobia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 77 (11.69%) | 12 / 75 (16.00%) | |
| occurrences (all) | 14 | 20 | |
| Amylase increased | | | |

| | | |
|--|-----------------|------------------|
| subjects affected / exposed | 6 / 77 (7.79%) | 4 / 75 (5.33%) |
| occurrences (all) | 9 | 21 |
| Aspartate aminotransferase increased | | |
| subjects affected / exposed | 9 / 77 (11.69%) | 14 / 75 (18.67%) |
| occurrences (all) | 17 | 21 |
| Bacterial test positive | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Biopsy prostate normal | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Blood albumin decreased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood alkaline phosphatase increased | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) |
| occurrences (all) | 3 | 1 |
| Blood bilirubin increased | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 4 / 75 (5.33%) |
| occurrences (all) | 0 | 5 |
| Blood calcium decreased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 1 |
| Blood cholesterol increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 5 / 75 (6.67%) |
| occurrences (all) | 1 | 6 |
| Blood creatine phosphokinase increased | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 3 / 75 (4.00%) |
| occurrences (all) | 7 | 3 |
| Blood creatinine increased | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 4 / 75 (5.33%) |
| occurrences (all) | 8 | 5 |
| Blood glucose increased | | |

| | | |
|---|----------------|-----------------|
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Blood lactate dehydrogenase increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 3 |
| Blood potassium increased | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Blood pressure increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Blood thyroid stimulating hormone increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Blood urea increased | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |
| Blood uric acid increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood urine present | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Creatinine renal clearance decreased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Ejection fraction decreased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 1 |
| Electrocardiogram QT prolonged | | |
| subjects affected / exposed | 5 / 77 (6.49%) | 8 / 75 (10.67%) |
| occurrences (all) | 7 | 22 |
| Electrocardiogram QRS complex prolonged | | |

| | | |
|--|----------------|----------------|
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |
| Electrocardiogram ST-T segment abnormal | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Electrocardiogram T wave abnormal | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Electrocardiogram abnormal | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 3 |
| Electrocardiogram T wave inversion | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) |
| occurrences (all) | 8 | 0 |
| Glucose urine present | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Haemoglobin increased | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| International normalised ratio increased | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Lipase increased | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 7 / 75 (9.33%) |
| occurrences (all) | 11 | 21 |
| Lymphocyte count decreased | | |
| subjects affected / exposed | 7 / 77 (9.09%) | 3 / 75 (4.00%) |
| occurrences (all) | 9 | 5 |
| Platelet count decreased | | |

| | | |
|-----------------------------------|------------------|------------------|
| subjects affected / exposed | 5 / 77 (6.49%) | 5 / 75 (6.67%) |
| occurrences (all) | 16 | 8 |
| Platelet count increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Tracheal aspiration procedure | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Transaminases increased | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |
| Troponin I increased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Urine analysis abnormal | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Urine ketone body present | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Urine leukocyte esterase positive | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Weight decreased | | |
| subjects affected / exposed | 34 / 77 (44.16%) | 30 / 75 (40.00%) |
| occurrences (all) | 67 | 62 |
| Weight increased | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 2 |
| White blood cell count decreased | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| White blood cells urine positive | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 2 |
| White blood cell count increased | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Corneal abrasion | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Fall | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 1 / 75 (1.33%) | |
| occurrences (all) | 3 | 1 | |
| Incision site pain | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| Post procedural pulmonary embolism | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Procedural nausea | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin abrasion | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 3 / 75 (4.00%) | |
| occurrences (all) | 2 | 3 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 2 / 75 (2.67%) | |
| occurrences (all) | 4 | 4 | |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |

| | | |
|--------------------------------|----------------|----------------|
| Cyanosis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Coronary artery disease | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 2 |
| Extrasystoles | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Left ventricular dysfunction | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Myocardial ischaemia | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Palpitations | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 5 / 75 (6.67%) |
| occurrences (all) | 1 | 6 |
| Sinus bradycardia | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Sinus tachycardia | | |
| subjects affected / exposed | 5 / 77 (6.49%) | 0 / 75 (0.00%) |
| occurrences (all) | 5 | 0 |
| Supraventricular extrasystoles | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 2 |
| Tachycardia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 2 |
| Toxic cardiomyopathy | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Ventricular fibrillation | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|---------------------|------------------------|--|
| Ventricular tachycardia subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Carotid artery aneurysm subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Balance disorder subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 | 1 / 75 (1.33%) 1 | |
| Carotid artery stenosis subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Cervical radiculopathy subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Cognitive disorder subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Dysaesthesia subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 6 / 77 (7.79%) 8 | 11 / 75 (14.67%) 14 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 5 / 77 (6.49%) 7 | 5 / 75 (6.67%) 6 | |
| Headache | | | |

| | | |
|-------------------------------|------------------|------------------|
| subjects affected / exposed | 17 / 77 (22.08%) | 19 / 75 (25.33%) |
| occurrences (all) | 29 | 24 |
| Essential tremor | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Hemiparesis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypogeusia | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Muscle spasticity | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lethargy | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Neuralgia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Paraesthesia | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 4 / 75 (5.33%) |
| occurrences (all) | 2 | 4 |
| Parkinson's disease | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Peripheral motor neuropathy | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 2 |
| Peripheral sensory neuropathy | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Sciatica | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 2 / 75 (2.67%) |
| occurrences (all) | 5 | 2 |
| Presyncope | | |

| | | | |
|--------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 4 / 75 (5.33%) | |
| occurrences (all) | 0 | 5 | |
| Tremor | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 4 / 75 (5.33%) | |
| occurrences (all) | 4 | 4 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 77 (10.39%) | 5 / 75 (6.67%) | |
| occurrences (all) | 13 | 5 | |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 2 / 75 (2.67%) | |
| occurrences (all) | 8 | 3 | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Lymphocytosis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 0 / 75 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Macrocytosis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Microcytosis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) | |
| occurrences (all) | 7 | 2 | |
| Neutrophilia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 8 / 75 (10.67%) | |
| occurrences (all) | 10 | 17 | |
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Ear discomfort | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear pain | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Tinnitus | | | |

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|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vertigo | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 2 / 75 (2.67%) | |
| occurrences (all) | 4 | 2 | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Cataract | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Dacryostenosis acquired | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Eye pain | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye irritation | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Periorbital oedema | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 2 | |

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| Photopsia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Retinal tear | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Retinal vascular occlusion | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Swelling of eyelid | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 4 / 75 (5.33%) | |
| occurrences (all) | 1 | 4 | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 4 / 75 (5.33%) | |
| occurrences (all) | 2 | 4 | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 77 (12.99%) | 18 / 75 (24.00%) | |
| occurrences (all) | 14 | 27 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Abdominal pain upper | | | |

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|-----------------------------|------------------|------------------|
| subjects affected / exposed | 13 / 77 (16.88%) | 10 / 75 (13.33%) |
| occurrences (all) | 21 | 15 |
| Anal fissure | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Anal incontinence | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Anorectal discomfort | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Apical granuloma | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Chapped lips | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Constipation | | |
| subjects affected / exposed | 20 / 77 (25.97%) | 9 / 75 (12.00%) |
| occurrences (all) | 21 | 9 |
| Dental caries | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 2 |
| Diarrhoea | | |
| subjects affected / exposed | 40 / 77 (51.95%) | 43 / 75 (57.33%) |
| occurrences (all) | 80 | 109 |
| Dry mouth | | |
| subjects affected / exposed | 9 / 77 (11.69%) | 10 / 75 (13.33%) |
| occurrences (all) | 11 | 10 |
| Duodenal ulcer | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Dyspepsia | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 11 / 75 (14.67%) |
| occurrences (all) | 4 | 13 |
| Dysphagia | | |

| | | |
|----------------------------------|----------------|----------------|
| subjects affected / exposed | 4 / 77 (5.19%) | 3 / 75 (4.00%) |
| occurrences (all) | 4 | 3 |
| Faeces pale | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Flatulence | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 2 / 75 (2.67%) |
| occurrences (all) | 4 | 2 |
| Gastritis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 1 |
| Gastrointestinal pain | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 2 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 5 / 77 (6.49%) | 1 / 75 (1.33%) |
| occurrences (all) | 6 | 1 |
| Gingival pain | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 2 |
| Gingival bleeding | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Glossodynia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 4 |
| Glossitis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) |
| occurrences (all) | 5 | 1 |
| Haematochezia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Haemorrhoids | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Inguinal hernia | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lip oedema | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Lip ulceration | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Melaena | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Mouth ulceration | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 2 / 75 (2.67%) |
| occurrences (all) | 3 | 2 |
| Nausea | | |
| subjects affected / exposed | 28 / 77 (36.36%) | 31 / 75 (41.33%) |
| occurrences (all) | 36 | 52 |
| Odynophagia | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 1 / 75 (1.33%) |
| occurrences (all) | 5 | 1 |
| Oesophageal stenosis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Oesophagitis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Oral discomfort | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oral disorder | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Oral dysaesthesia | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 5 / 75 (6.67%) |
| occurrences (all) | 4 | 5 |
| Oral pain | | |

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|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 6 / 77 (7.79%) | 6 / 75 (8.00%) | |
| occurrences (all) | 8 | 12 | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 3 / 75 (4.00%) | |
| occurrences (all) | 0 | 3 | |
| Stomatitis | | | |
| subjects affected / exposed | 22 / 77 (28.57%) | 16 / 75 (21.33%) | |
| occurrences (all) | 50 | 25 | |
| Tongue discolouration | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Tongue discomfort | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Tooth disorder | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Toothache | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 6 / 75 (8.00%) | |
| occurrences (all) | 4 | 6 | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 77 (16.88%) | 15 / 75 (20.00%) | |
| occurrences (all) | 21 | 22 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 3 / 75 (4.00%) | |
| occurrences (all) | 1 | 3 | |

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|---|----------------|----------------|--|
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 4 / 75 (5.33%) | |
| occurrences (all) | 4 | 4 | |
| Acne | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blister | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 2 | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) | |
| occurrences (all) | 4 | 1 | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Dry skin | | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 5 / 75 (6.67%) | |
| occurrences (all) | 6 | 6 | |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 3 | |
| Eczema | | | |

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| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 3 |
| Erythema | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 3 / 75 (4.00%) |
| occurrences (all) | 1 | 3 |
| Hyperhidrosis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Hyperkeratosis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 3 / 75 (4.00%) |
| occurrences (all) | 3 | 3 |
| Ingrowing nail | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Ischaemic skin ulcer | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Ingrown hair | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Night sweats | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Nail bed bleeding | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Onychoclasia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | | |
| subjects affected / exposed | 22 / 77 (28.57%) | 26 / 75 (34.67%) |
| occurrences (all) | 45 | 48 |
| Palmoplantar keratoderma | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |

| | | |
|-----------------------------|----------------|----------------|
| Papule | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Plantar erythema | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Photosensitivity reaction | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |
| Petechiae | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Pruritus | | |
| subjects affected / exposed | 7 / 77 (9.09%) | 5 / 75 (6.67%) |
| occurrences (all) | 9 | 5 |
| Rash | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 6 / 75 (8.00%) |
| occurrences (all) | 5 | 10 |
| Rash erythematous | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Rash maculo-papular | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 2 |
| Rash pruritic | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Skin disorder | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Skin exfoliation | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 1 |
| Skin hyperpigmentation | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |

| | | | |
|-----------------------------|----------------|----------------|--|
| Skin haemorrhage | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 1 | 1 | |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 6 | |
| Skin induration | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 4 | |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin toxicity | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 3 / 75 (4.00%) | |
| occurrences (all) | 0 | 3 | |
| Vitiligo | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Haematuria | | | |

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|--|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 3 / 75 (4.00%) 5 | |
| Dysuria subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 3 | 1 / 75 (1.33%) 1 | |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Renal cyst subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Proteinuria subjects affected / exposed occurrences (all) | 26 / 77 (33.77%) 93 | 35 / 75 (46.67%) 169 | |
| Leukocyturia subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 3 | |
| Renal failure subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Renal impairment subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Urinary tract obstruction subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 75 (2.67%) 2 | |
| Hypoparathyroidism subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Inappropriate antidiuretic hormone secretion | | | |

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| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thyroid haemorrhage | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Amyotrophy | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Arthritis | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) | |
| occurrences (all) | 4 | 1 | |
| Back pain | | | |
| subjects affected / exposed | 12 / 77 (15.58%) | 14 / 75 (18.67%) | |
| occurrences (all) | 14 | 17 | |
| Bone pain | | | |
| subjects affected / exposed | 5 / 77 (6.49%) | 2 / 75 (2.67%) | |
| occurrences (all) | 7 | 2 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 22 / 77 (28.57%) | 29 / 75 (38.67%) | |
| occurrences (all) | 39 | 45 | |
| Flank pain | | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 0 / 75 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Coccydynia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Intervertebral disc displacement | | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypercreatinaemia | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Groin pain | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 4 / 75 (5.33%) |
| occurrences (all) | 0 | 4 |
| Joint stiffness | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Muscular weakness | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 6 / 75 (8.00%) |
| occurrences (all) | 1 | 7 |
| Muscle spasms | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 4 / 75 (5.33%) |
| occurrences (all) | 8 | 4 |
| Joint swelling | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 2 |
| Musculoskeletal chest pain | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 6 / 75 (8.00%) |
| occurrences (all) | 3 | 9 |
| Musculoskeletal pain | | |
| subjects affected / exposed | 15 / 77 (19.48%) | 10 / 75 (13.33%) |
| occurrences (all) | 25 | 13 |
| Musculoskeletal stiffness | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |
| Myalgia | | |
| subjects affected / exposed | 17 / 77 (22.08%) | 18 / 75 (24.00%) |
| occurrences (all) | 33 | 25 |
| Pain in extremity | | |
| subjects affected / exposed | 11 / 77 (14.29%) | 9 / 75 (12.00%) |
| occurrences (all) | 17 | 19 |
| Osteoarthritis | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 75 (2.67%) | |
| occurrences (all) | 0 | 2 | |
| Neck pain | | | |
| subjects affected / exposed | 11 / 77 (14.29%) | 10 / 75 (13.33%) | |
| occurrences (all) | 15 | 11 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Periarthritis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) | |
| occurrences (all) | 2 | 3 | |
| Pain in jaw | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 1 / 75 (1.33%) | |
| occurrences (all) | 7 | 1 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Plantar fasciitis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sarcopenia | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Limb discomfort | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Abscess oral | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Asymptomatic bacteriuria | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) | |
| occurrences (all) | 0 | 1 | |

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|-----------------------------|----------------|----------------|
| Rash pustular | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Bronchiolitis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Bronchitis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 2 / 75 (2.67%) |
| occurrences (all) | 2 | 2 |
| COVID-19 pneumonia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Cystitis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 75 (2.67%) |
| occurrences (all) | 1 | 3 |
| Cellulitis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 4 | 0 |
| Device related infection | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Diverticulitis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Eyelid infection | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Fungal infection | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Folliculitis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 2 |
| Furuncle | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |

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|-----------------------------------|----------------|----------------|
| Gastroenteritis | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 1 / 75 (1.33%) |
| occurrences (all) | 4 | 1 |
| Gastroenteritis viral | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gingivitis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Helicobacter infection | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Herpes zoster | | |
| subjects affected / exposed | 4 / 77 (5.19%) | 0 / 75 (0.00%) |
| occurrences (all) | 5 | 0 |
| Influenza | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 1 |
| Oral candidiasis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 4 | 0 |
| Localised infection | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 3 |
| Lower respiratory tract infection | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Lymph gland infection | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nasopharyngitis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 3 / 75 (4.00%) |
| occurrences (all) | 3 | 5 |
| Oesophageal candidiasis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |

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| Laryngitis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Oral fungal infection | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oral herpes | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Paronychia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pharyngitis | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Pneumonia | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 3 / 75 (4.00%) |
| occurrences (all) | 4 | 3 |
| Pneumonia bacterial | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pyuria | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Bacteriuria | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Rhinitis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Sialoadenitis | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 1 |
| Sinusitis | | |
| subjects affected / exposed | 5 / 77 (6.49%) | 3 / 75 (4.00%) |
| occurrences (all) | 6 | 4 |

| | | | |
|---|---------------------|---------------------|--|
| Tooth abscess subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 | 1 / 75 (1.33%) 1 | |
| Tooth infection subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 2 | 1 / 75 (1.33%) 1 | |
| Tracheitis subjects affected / exposed occurrences (all) | 3 / 77 (3.90%) 3 | 0 / 75 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 | 1 / 75 (1.33%) 2 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 77 (6.49%) 8 | 4 / 75 (5.33%) 4 | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 3 | |
| Viral infection subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Metabolism and nutrition disorders Abnormal loss of weight subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 0 / 75 (0.00%) 0 | |
| Acidosis subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Cachexia subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Decreased appetite | | | |

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| subjects affected / exposed | 22 / 77 (28.57%) | 26 / 75 (34.67%) |
| occurrences (all) | 40 | 38 |
| Dehydration | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Diabetes mellitus | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 |
| Dyslipidaemia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hyperamylasaemia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypercalcaemia | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 2 / 75 (2.67%) |
| occurrences (all) | 2 | 7 |
| Hypercholesterolaemia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 2 |
| Hyperglycaemia | | |
| subjects affected / exposed | 5 / 77 (6.49%) | 7 / 75 (9.33%) |
| occurrences (all) | 8 | 8 |
| Hyperkalaemia | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 2 / 75 (2.67%) |
| occurrences (all) | 3 | 2 |
| Hyperphosphataemia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypertriglyceridaemia | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 3 / 75 (4.00%) |
| occurrences (all) | 10 | 3 |
| Hyperuricaemia | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 1 |
| Hypoglycaemia | | |

| | | |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 3 / 77 (3.90%) | 0 / 75 (0.00%) |
| occurrences (all) | 3 | 0 |
| Hypocalcaemia | | |
| subjects affected / exposed | 12 / 77 (15.58%) | 8 / 75 (10.67%) |
| occurrences (all) | 31 | 10 |
| Hypoalbuminaemia | | |
| subjects affected / exposed | 7 / 77 (9.09%) | 0 / 75 (0.00%) |
| occurrences (all) | 8 | 0 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 10 / 77 (12.99%) | 5 / 75 (6.67%) |
| occurrences (all) | 14 | 7 |
| Hypokalaemia | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 8 / 75 (10.67%) |
| occurrences (all) | 9 | 16 |
| Hyponatraemia | | |
| subjects affected / exposed | 6 / 77 (7.79%) | 6 / 75 (8.00%) |
| occurrences (all) | 9 | 8 |
| Hypophagia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 1 |
| Hypoproteinaemia | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Metabolic alkalosis | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypophosphataemia | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 3 / 75 (4.00%) |
| occurrences (all) | 3 | 3 |
| Vitamin B12 deficiency | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 01 December 2015 | Amendment 01: Added cautionary text to Section 9.4.5.1 regarding the use of lenvatinib with CYP3A4 substrates known to have a narrow therapeutic index to align with VHP recommendations. Added exploratory endpoint of OS inadvertently omitted from the final protocol |
| 31 May 2016 | Amendment 02: Added exclusion criterion 14 to exclude enrollment of subjects with bleeding or thrombotic disorders. Added guidance for management of confirmed hypertension with systolic BP ≥ 140 mmHg up to <160 mmHg or diastolic BP ≥ 90 mmHg up to <100 mmHg as required by the French Health Authority. |
| 13 February 2017 | Amendment 03: Clarified throughout the protocol that study was changed from a 3-arm to a 2-arm design, with randomization in a 1:1 ratio and approximately 60 subjects assigned per treatment arm (total N = 120). starting doses of lenvatinib were changed from 24 mg, 20 mg, and 14 mg (with uptitration) to 24 mg and 18 mg (without uptitration) throughout. Primary endpoint for ORR changed from 6-month calendar time point (ORR6M) to 24-week time point (ORR24wk) for clarity. Clarified that the analysis of the primary endpoint (ORR24wk) was to be based on a noninferiority test on the odds ratio, with a noninferiority margin of 0.4. Clarified that analyses of PK and PK/pharmacodynamic data would include data from subjects treated prior to Amendment 03. Secondary objective to evaluate PK/pharmacodynamic was revised to include modeling using a mechanistically based approach, if possible, in response to EMA's request to modify PK and biomarker sampling. |
| 16 February 2018 | Amendment 04: Formalized proposed changes written for regulatory purposes in response to VHP comments on Amendment 03. Adjusted statistical methodology to demonstrate the noninferiority of the lenvatinib 18-mg arm as compared to the 24-mg arm, and to implement corresponding changes in the sample size. Modifications were made to the management of hypertension and proteinuria to conform with other ongoing studies for lenvatinib. Clarified exclusion criteria regarding surgery and cardiovascular impairment. Clarified that subjects would receive study drug until subject requested to discontinue or was lost to follow-up. |
| 21 May 2019 | Amendment 05: Clarified that subjects would continue to receive blinded study drug after the Randomization Phase ended (when last subject enrolled had completed the Week 24 tumor assessments or had discontinued study treatment before Week 24) until the primary analysis had been completed. |
| 09 January 2020 | Amendment 06: Clarified that the data cutoff for the primary analysis refers to the statistical end of the study for analysis purposes (end of the Randomization Phase) and that the End of Study refers to the last subject last visit, after which all subjects will have completed their Off-treatment visits. Clarified transition procedures for subjects who discontinued lenvatinib. Clarified that follow-up assessments were not performed after the data cutoff for the primary analysis. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| None reported |
|---------------|

Notes: