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: 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[4]	0[5]		
Units: subjects				
number (not applicable)				

Notes:

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

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

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[6]

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:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: 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 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: 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: 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: 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: 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: 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: 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 Disatolic Input Rate Estimates from Base/Final PK/PD Blood Pressure Model

End point title	Drug Effect on Systolic and Disatolic Input Rate Estimates 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: 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 atleast 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 atleast 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 atleast 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 atleast 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 atleast 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 atleast 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 atleast 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

No statistical analyses for this end point

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	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 77 (27.27%)	18 / 75 (24.00%)	
occurrences (all)	51	34	
Axillary pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	3 / 77 (3.90%)	1 / 75 (1.33%)	
occurrences (all)	3	1	
Chest pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 77 (1.30%)	3 / 75 (4.00%)	
occurrences (all)	1	5	
Discomfort			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Early satiety			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	2 / 77 (2.60%)	0 / 75 (0.00%)	
occurrences (all)	2	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	12 / 77 (15.58%)	16 / 75 (21.33%)	
occurrences (all)	19	25	
Pain			
subjects affected / exposed	4 / 77 (5.19%)	3 / 75 (4.00%)	
occurrences (all)	6	3	
Pyrexia			
subjects affected / exposed	7 / 77 (9.09%)	4 / 75 (5.33%)	
occurrences (all)	9	4	
Temperature intolerance			
subjects affected / exposed	0 / 77 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 77 (1.30%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Erectile dysfunction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Genital haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Menstruation irregular			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	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	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Carotid artery aneurysm			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	2 / 77 (2.60%)	1 / 75 (1.33%)	
occurrences (all)	2	1	
Carotid artery stenosis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Cervical radiculopathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Cognitive disorder			
subjects affected / exposed	0 / 77 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Disturbance in attention			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Dysaesthesia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	6 / 77 (7.79%)	11 / 75 (14.67%)	
occurrences (all)	8	14	
Dysgeusia			
subjects affected / exposed	5 / 77 (6.49%)	5 / 75 (6.67%)	
occurrences (all)	7	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			

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	

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			

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			

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	

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			

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		
Onychoclasis				
subjects affected / exposed	1 / 77 (1.30%)	0 / 75 (0.00%)		
occurrences (all)	1	0		
Palmar-plantar erythrodysaesthesia 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			

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

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	

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	

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	

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

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.

None reported

Notes: