Clinical trial results:
Phase II, Multicenter, Open-label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology.

Summary

EudraCT number	2007-005933-12
Trial protocol	FR PL GB IT
Global end of trial date	29 March 2019

Results information

Result version number	v2 (current)
This version publication date	16 April 2020
First version publication date	19 December 2018
Version creation reason	• New data added to full data set Full Data Set
Summary attachment (see zip file)	E7080-G000-201 CSR Synopsis (E7080-G000-201-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	E7080-G000-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00784303
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, New Jersey 07677
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In subjects with medullary thyroid cancer [MTC] or radioiodine (131*I) refractory/resistant differentiated thyroid cancer[DTC]:

- Determine the effect of E7080 on the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) by independent imaging review (IIR).

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. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	United States: 78
Worldwide total number of subjects	162
EEA total number of subjects	69

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)	115
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

162 subjects were screened for entry into the study, of which 45 were screening failures and 117 enrolled in the study and were treated.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DTC Cohort

Arm description:

Subjects with radioiodine (131 I)-refractory/resistant DTC received 24 milligram (mg) lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	LENVIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily, or 10 mg lenvatinib orally twice daily (20 mg total). 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Arm title	MTC Cohort

Arm description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	LENVIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily given continuously in 28-day treatment cycles.

Number of subjects in period 1[1]	DTC Cohort	MTC Cohort
Started	58	59
Completed	58	59

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects in the Baseline period are those who received the study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	DTC Cohort
Reporting group description:	
Subjects with radioiodine (131 I)-refractory/resistant DTC received 24 milligram (mg) lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.	
Reporting group title	MTC Cohort
Reporting group description:	
Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.	

Reporting group values	DTC Cohort	MTC Cohort	Total
Number of subjects	58	59	117
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.9	51.6	
standard deviation	± 9.49	± 14.11	-
Gender categorical			
Units: Subjects			
Female	24	22	46
Male	34	37	71

End points

End points reporting groups

Reporting group title	DTC Cohort

Reporting group description:

Subjects with radioiodine (131 I)-refractory/resistant DTC received 24 milligram (mg) lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Reporting group title	MTC Cohort

Reporting group description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

Primary: ORR

End point title	ORR[1]

End point description:

ORR was the percentage (%) of subjects with best overall response (BOR) of complete response (CR) and partial response (PR) based on modified RECIST 1.0 for target lesions using magnetic resonance imaging/computed tomography (MRI/CT) scans, as determined by IIR. CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter. ORR (CR+PR), was presented with 2-sided 95% confidence interval (CI) by the method of Clopper and Pearson. The Intent to Treat (ITT) Population included all subjects who received at least one dose of the study drug and was the primary analysis set used for efficacy analyses.

End point type	Primary

End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, subject’s choice to stop study treatment, or up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

Notes:

[1] - 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 the end point.

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Percentage of subjects				
number (confidence interval 90%)	50.0 (36.6 to 63.4)	35.6 (23.6 to 49.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK): Steady State Area Under the Plasma Concentration Curve (AUC)

End point title	Plasma Pharmacokinetics (PK): Steady State Area Under the Plasma Concentration Curve (AUC)

End point description:

Up to 9 samples per subject were obtained at specific time points. Plasma concentrations of lenvatinib were analyzed using standard analysis methods. Due to the sparse PK sampling in this study, the data were pooled with data from other Phase 1 studies conducted in subjects with solid tumors for PK model development and covariate analysis. Individual exposure (steady state AUC) to lenvatinib in MTC and DTC subjects in this study was derived based on the individual predicted steady state AUC from the final PK model. Only data for subjects taking 24 mg lenvatinib daily were reported (subjects taking 20 mg lenvatinib daily were not included in this data set). PK population included all subjects who received the 24 mg daily lenvatinib dose and had concentration values above the limit of quantification and non-missing PK sampling/dose time.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (predose and at 0.5 and 2 hours postdose), Cycle 1 Day 8 (predose), Cycle 2 Day 1 (predose and at 0.5 and 2 hours postdose), and Cycle 3 Day 1 (predose and at 2 hours postdose) (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	56		
Units: nanogram*hour per milliliter (ng·h/mL)				
median (full range (min-max))	3840 (1610 to 6960)	3350 (1040 to 6840)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Free Thyroxine (T4)

End point title	Change From Baseline in Free Thyroxine (T4)

End point description:

Blood samples to measure free T4 were collected at Screening (Baseline), Cycle 1 Day 15 (MTC cohort), Day 1 of Cycles 2 to 20, and Final Visit. Changes in free T4 concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 1 Day 15 and Cycle 20 Day 1 because no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: picomole/liter (pmol/L)				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n= 0, 1)	0 (± 0)	-3.80 (± 99999)		
Cycle 2 Day 1 (n= 53, 57)	-0.46 (± 5.149)	-0.86 (± 3.913)		
Cycle 3 Day 1 (n= 50, 54)	-0.92 (± 4.985)	-1.00 (± 4.028)		
Cycle 4 Day 1 (n= 48, 50)	-1.05 (± 5.581)	0.34 (± 4.192)		
Cycle 5 Day 1 (n= 46, 47)	-1.03 (± 5.563)	-0.46 (± 3.878)		
Cycle 6 Day 1 (n= 43, 45)	-2.19 (± 5.373)	-0.17 (± 4.719)		
Cycle 7 Day 1 (n= 39, 40)	-2.32 (± 5.098)	-1.07 (± 5.403)		
Cycle 8 Day 1 (n= 37, 37)	-1.74 (± 5.504)	-1.13 (± 5.691)		
Cycle 9 Day 1 (n= 30, 37)	-0.39 (± 5.295)	0.52 (± 5.213)		
Cycle 10 Day 1 (n= 30, 32)	-0.26 (± 6.397)	1.33 (± 6.319)		
Cycle 11 Day 1 (n= 30, 26)	-0.27 (± 6.384)	0.30 (± 5.551)		
Cycle 12 Day 1 (n= 30, 21)	-1.60 (± 6.331)	-0.43 (± 5.380)		
Cycle 13 Day 1 (n= 29, 19)	-0.09 (± 5.416)	0.07 (± 4.347)		
Cycle 14 Day 1 (n= 27, 14)	-0.54 (± 5.772)	-0.82 (± 6.394)		
Cycle 15 Day 1 (n= 26, 10)	0.63 (± 6.703)	-1.01 (± 5.505)		
Cycle 16 Day 1 (n= 24, 9)	-0.98 (± 7.150)	0.60 (± 4.142)		
Cycle 17 Day 1 (n= 17, 6)	1.20 (± 7.075)	0.45 (± 3.528)		
Cycle 18 Day 1 (n= 10, 6)	0.38 (± 4.648)	2.17 (± 4.831)		
Cycle 19 Day 1 (n= 4, 2)	-0.65 (± 4.042)	3.25 (± 4.596)		
Cycle 20 Day 1 (n= 0, 1)	0 (± 0)	5.20 (± 99999)		
Final Visit/Study Termination (n= 21, 22)	-0.36 (± 6.175)	1.27 (± 4.584)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Free Thyroid Stimulating Hormone (TSH)

End point title	Change From Baseline in Free Thyroid Stimulating Hormone (TSH)

End point description:

Blood samples to measure free TSH were collected at Screening (Baseline), Cycle 1 Day 15 (MTC cohort), Day 1 of Cycles 2 to 20, and Final Visit. Changes in free TSH concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were

included. For any free TSH result that was reported as <0.008 mIU/L, 0.004 mIU/L was used for calculating summary statistics. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 1 Day 15 and Cycle 20 Day 1 because no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Milli international units per litre				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n= 0, 1)	0 (± 0)	2.8030 (± 99999)		
Cycle 2 Day 1 (n= 41, 55)	0.4779 (± 3.07666)	4.1585 (± 7.34946)		
Cycle 3 Day 1 (n= 38, 52)	0.5161 (± 2.79122)	5.5788 (± 13.76600)		
Cycle 4 Day 1 (n= 37, 48)	0.6296 (± 2.29420)	2.8751 (± 6.50098)		
Cycle 5 Day 1 (n= 35, 45)	0.5024 (± 2.22721)	3.7098 (± 6.60386)		
Cycle 6 Day 1 (n= 32, 44)	0.8603 (± 3.09079)	3.9822 (± 10.65477)		
Cycle 7 Day 1 (n= 30, 40)	0.6660 (± 2.08608)	8.4308 (± 22.51715)		
Cycle 8 Day 1 (n= 30, 37)	0.2118 (± 3.16324)	11.4131 (± 32.65896)		
Cycle 9 Day 1 (n= 25, 37)	0.1270 (± 3.53020)	6.6620 (± 18.89412)		
Cycle 10 Day 1 (n= 26, 32)	-0.3277 (± 2.87114)	6.1934 (± 17.99762)		
Cycle 11 Day 1 (n= 25, 26)	-0.2940 (± 3.28192)	2.7928 (± 9.42343)		
Cycle 12 Day 1 (n= 25, 21)	0.3500 (± 5.43946)	5.1879 (± 14.81415)		
Cycle 13 Day 1 (n= 25, 19)	-0.2799 (± 3.31518)	2.0983 (± 7.03903)		
Cycle 14 Day 1 (n= 23, 14)	-0.6232 (± 3.09954)	9.6490 (± 32.48910)		
Cycle 15 Day 1 (n= 22, 10)	-0.5911 (± 3.21447)	0.9955 (± 4.93549)		
Cycle 16 Day 1 (n= 20, 9)	-0.3396 (± 3.68903)	0.2971 (± 3.33103)		
Cycle 17 Day 1 (n= 14, 7)	-1.0352 (± 3.92286)	7.4624 (± 16.18545)		
Cycle 18 Day 1 (n= 8, 6)	0.0331 (± 0.24520)	4.1232 (± 7.01461)		
Cycle 19 Day 1 (n= 4, 2)	0.7805 (± 1.87674)	-0.2080 (± 0.29698)		
Cycle 20 Day 1 (n= 0, 1)	0 (± 0)	0.0000 (± 99999)		

Final Visit/Study Termination (n= 17, 20)	1.0281 (± 2.07161)	3.4905 (± 7.39625)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Concentrations of Thyroglobulin (DTC Only)

End point title	Percent Change From Baseline in Concentrations of Thyroglobulin (DTC Only)[2]

End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1 (Baseline), Day 1 of Cycles 2 to 19, Final Visit, and were analyzed for thyroglobulin concentration. Percent changes in thyroglobulin concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 19, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for the end point.

End point values	DTC Cohort			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: percent change				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 47)	-62.21 (± 39.997)			
Cycle 3 Day 1 (n= 44)	-77.80 (± 22.278)			
Cycle 4 Day 1 (n= 41)	-79.25 (± 26.639)			
Cycle 5 Day 1 (n= 40)	-76.00 (± 25.085)			
Cycle 6 Day 1 (n= 40)	-20.36 (± 373.190)			
Cycle 7 Day 1 (n= 30)	-73.38 (± 45.489)			
Cycle 8 Day 1 (n= 29)	-79.96 (± 27.461)			
Cycle 9 Day 1 (n= 21)	-73.98 (± 31.366)			
Cycle 10 Day 1 (n= 26)	-78.26 (± 25.524)			
Cycle 11 Day 1 (n= 28)	-75.54 (± 37.327)			

Cycle 12 Day 1 (n= 26)	-73.51 (± 46.397)			
Cycle 13 Day 1 (n= 26)	-74.05 (± 37.091)			
Cycle 14 Day 1 (n= 24)	-78.70 (± 17.348)			
Cycle 15 Day 1 (n= 23)	-80.28 (± 16.029)			
Cycle 16 Day 1 (n= 22)	-76.38 (± 27.736)			
Cycle 17 Day 1 (n= 15)	-62.99 (± 38.740)			
Cycle 18 Day 1 (n= 9)	-72.67 (± 27.226)			
Cycle 19 Day 1 (n= 4)	-50.65 (± 46.900)			
Final Visit/Study Termination (n= 1)	-68.60 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Concentrations of Calcitonin (MTC Only)

End point title	Percent Change From Baseline in Concentrations of Calcitonin (MTC Only)[3]

End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1(Baseline), Day 1 of Cycles 2 to 20, Final Visit, and were analyzed for calcitonin concentration. Percent changes in calcitonin concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (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: Only descriptive data was planned to be analyzed for the end point.

End point values	MTC Cohort			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percent change				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 51)	-42.27 (± 38.754)			
Cycle 3 Day 1 (n= 47)	-48.11 (± 30.976)			
Cycle 4 Day 1 (n= 44)	-44.54 (± 38.794)			

Cycle 5 Day 1 (n= 40)	-49.97 (± 34.634)			
Cycle 6 Day 1 (n= 39)	-41.73 (± 46.653)			
Cycle 7 Day 1 (n= 34)	-38.18 (± 62.721)			
Cycle 8 Day 1 (n= 33)	-47.29 (± 46.101)			
Cycle 9 Day 1 (n= 29)	-37.52 (± 72.588)			
Cycle 10 Day 1 (n= 29)	-39.57 (± 60.118)			
Cycle 11 Day 1 (n= 24)	-42.68 (± 61.797)			
Cycle 12 Day 1 (n= 19)	-29.25 (± 105.440)			
Cycle 13 Day 1 (n= 17)	-36.26 (± 89.612)			
Cycle 14 Day 1 (n= 12)	-18.16 (± 148.928)			
Cycle 15 Day 1 (n= 9)	-65.26 (± 24.553)			
Cycle 16 Day 1 (n= 8)	-64.24 (± 30.394)			
Cycle 17 Day 1 (n= 7)	-66.03 (± 23.777)			
Cycle 18 Day 1 (n= 6)	-64.57 (± 27.982)			
Cycle 19 Day 1 (n= 2)	-44.30 (± 18.668)			
Cycle 20 Day 1 (n= 1)	-29.40 (± 99999)			
Final Visit/Study Termination (n= 4)	-36.70 (± 28.296)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Concentrations of Carcinoembryonic Antigen (CEA) (MTC Only)

End point title	Percent Change From Baseline in Concentrations of Carcinoembryonic Antigen (CEA) (MTC Only)[4]

End point description:

Blood samples were collected at Cycle 1 Day 1(Baseline), Day 1 of Cycles 2 to 20, Final Visit, and were analyzed for CEA concentration. Percent changes in CEA concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for the end point.

End point values	MTC Cohort			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percent change				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 54)	-26.07 (± 45.864)			
Cycle 3 Day 1 (n= 49)	-37.68 (± 42.236)			
Cycle 4 Day 1 (n= 46)	-41.49 (± 48.035)			
Cycle 5 Day 1 (n= 42)	-44.62 (± 42.138)			
Cycle 6 Day 1 (n= 42)	-41.91 (± 47.388)			
Cycle 7 Day 1 (n= 36)	-41.39 (± 45.677)			
Cycle 8 Day 1 (n= 34)	-42.89 (± 47.818)			
Cycle 9 Day 1 (n= 30)	-49.31 (± 32.185)			
Cycle 10 Day 1 (n= 30)	-47.35 (± 31.621)			
Cycle 11 Day 1 (n= 25)	-51.75 (± 29.671)			
Cycle 12 Day 1 (n= 20)	-49.91 (± 32.597)			
Cycle 13 Day 1 (n= 18)	-46.44 (± 35.967)			
Cycle 14 Day 1 (n= 13)	-47.98 (± 38.324)			
Cycle 15 Day 1 (n= 10)	-56.62 (± 34.051)			
Cycle 16 Day 1 (n= 9)	-59.83 (± 34.762)			
Cycle 17 Day 1 (n= 7)	-53.80 (± 37.981)			
Cycle 18 Day 1 (n= 6)	-46.00 (± 39.905)			
Cycle 19 Day 1 (n= 2)	-45.65 (± 18.738)			
Cycle 20 Day 1 (n= 1)	-61.40 (± 99999)			
Final Visit/Study Termination (n= 4)	-29.43 (± 31.453)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Concentrations of Cytochrome C (CytoC)

End point title	Change From Baseline in Concentrations of Cytochrome C (CytoC)

End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1(Baseline), Cycle 1 Day 8, Cycle 2 Days 1,8 &15, Cycles 3 to 9,11,13 Day 1, Final Visit, and analyzed for CytoC concentration. Changes in CytoC concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. For results reported as below quantifiable level (BQL), zero was used for calculating summary statistics. If more than 50% of the results at a visit were BQL, then only 'n', 'minimum' and 'maximum' were calculated for summary statistics. All subjects who received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 2 Day 1, for MTC cohort at Cycle 2 Day 15, Day 1 of Cycle 11 and 13 because no subject was evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Cycle 1 (Day 8), Cycle 2 (Days 1, 8 and 15), Cycles 3, 4, 5, 6, 7, 8, 9, 11, & 13 (Day 1), and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 8 (n= 52, 52)	155.57 (± 825.091)	502.84 (± 2146.291)		
Cycle 2 Day 1 (n= 0, 1)	0 (± 0)	1679.40 (± 99999)		
Cycle 2 Day 8 (n= 46, 49)	-218.45 (± 591.217)	374.46 (± 2279.207)		
Cycle 2 Day 15 (n= 1, 0)	-215.50 (± 99999)	0 (± 0)		
Cycle 3 Day 1 (n= 44, 47)	-175.43 (± 435.635)	311.85 (± 2363.970)		
Cycle 4 Day 1 (n= 19, 17)	1.38 (± 268.354)	63.01 (± 1738.149)		
Cycle 5 Day 1 (n= 15, 13)	-21.32 (± 85.469)	1078.85 (± 3793.235)		
Cycle 6 Day 1 (n= 14, 10)	721.58 (± 1234.215)	1411.29 (± 3855.502)		
Cycle 7 Day 1 (n= 10, 7)	858.05 (± 1383.962)	2184.30 (± 4689.181)		
Cycle 8 Day 1 (n= 10, 5)	1358.51 (± 1364.706)	451.36 (± 254.305)		
Cycle 9 Day 1 (n= 6, 5)	1356.40 (± 913.685)	459.38 (± 1572.717)		
Cycle 11 Day 1 (n= 1, 0)	139.60 (± 99999)	0 (± 0)		
Cycle 13 Day 1 (n= 1, 0)	129.60 (± 99999)	0 (± 0)		
Final Visit/Study Termination (n= 19, 23)	249.31 (± 765.148)	-45.97 (± 1294.476)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Concentrations of M-30 Neo-Antigen

End point title	Change From Baseline in Concentrations of M-30 Neo-Antigen

End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1(Baseline), Cycle 1 Day 8, Cycle 2 Days 1,8 &15, Cycles 3 to 9,11,13 Day 1, Final Visit, and analyzed for M-30 concentration. Changes in M-30 concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. For results reported as BQL, zero was used for calculating summary statistics. If more than 50% of the results at a visit were BQL, then only 'n', 'minimum' and 'maximum' were calculated for summary statistics. All subjects who received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 2 Day 1, for MTC cohort at Cycle 2 Day 15, Day 1 of Cycle 11 and 13 because no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

Cycle 1 (Day 8), Cycle 2 (Days 1, 8 & 15), Cycles 3, 4, 5, 6, 7, 8, 9, 11 & 13 (Day 1) and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)				
Cycle 1 Day 8 (n= 52, 52)	-5.22 (± 108.639)	46.32 (± 197.509)		
Cycle 2 Day 1 (n= 0, 1)	0 (± 0)	-77.80 (± 99999)		
Cycle 2 Day 8 (n= 46, 49)	-26.41 (± 257.723)	-49.33 (± 289.525)		
Cycle 2 Day 15 (n= 1, 0)	35.30 (± 99999)	0 (± 0)		
Cycle 3 Day 1 (n= 44, 47)	19.70 (± 296.010)	90.21 (± 314.343)		
Cycle 4 Day 1 (n= 19, 17)	-7.89 (± 336.124)	-97.53 (± 296.832)		
Cycle 5 Day 1 (n= 15, 13)	-24.83 (± 397.337)	-161.36 (± 265.548)		
Cycle 6 Day 1 (n= 14, 10)	-99.30 (± 321.554)	-161.30 (± 214.299)		
Cycle 7 Day 1 (n= 10, 7)	-168.50 (± 378.071)	-52.79 (± 129.671)		
Cycle 8 Day 1 (n= 10, 5)	-180.22 (± 386.682)	-92.44 (± 57.828)		
Cycle 9 Day 1 (n= 6, 5)	-111.92 (± 189.411)	-85.22 (± 161.751)		
Cycle 11 Day 1 (n= 1, 0)	55.00 (± 99999)	0 (± 0)		
Cycle 13 Day 1 (n= 1, 0)	-263.50 (± 99999)	0 (± 0)		
Final Visit/Study Termination (n= 19, 23)	-151.73 (± 322.159)	-158.99 (± 355.903)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Concentrations of Activated Caspase 3/7 (Casp 3/7)

End point title	Change From Baseline in Concentrations of Activated Caspase 3/7 (Casp 3/7)

End point description:

Blood samples to obtain serum collected at Cycle 1 Day 1(Baseline), Cycle 1 Day 8, Cycle 2 Days 1, 8, 15, Cycles 3 to 9, 11, 13(Day 1), Final Visit, analyzed for Casp 3/7 concentration. Changes in Casp 3/7 concentration values from baseline were calculated. Only subjects with both baseline and relevant visit values were included. Concentrations of Casp 3/7 were BQL for most subjects at most time points. For results reported as BQL, zero used for calculating summary statistics. If >50% of results at visit were BQL, then only 'n', 'minimum' and 'maximum' were calculated for summary statistics. Subjects received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values included. Data not reported for DTC cohort at Cycle 2 Day 1, MTC cohort at Cycle 2 Day 15, Day 1 of Cycle 11 and 13 as no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space filler.

End point type	Secondary

End point timeframe:

Cycle 1 (Day 8), Cycle 2 (Days 1, 8, & 15), Cycles 3, 4, 5, 6, 7, 8, 9, 11, & 13 (Day 1) and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: U/W				
arithmetic mean (standard deviation)				
Cycle 1 Day 8 (n= 50, 52)	99999 (± 99999)	0.0030 (± 0.00610)		
Cycle 2 Day 1 (n= 0, 1)	0 (± 0)	0.0080 (± 99999)		
Cycle 2 Day 8 (n= 44, 49)	99999 (± 99999)	0.0039 (± 0.00822)		
Cycle 2 Day 15 (n= 1, 0)	0.0110 (± 99999)	0 (± 0)		
Cycle 3 Day 1 (n= 42, 47)	99999 (± 99999)	0.0026 (± 0.00691)		
Cycle 4 Day 1 (n= 18, 17)	99999 (± 99999)	0.0019 (± 0.00743)		
Cycle 5 Day 1 (n= 15, 13)	99999 (± 99999)	0.0042 (± 0.00666)		
Cycle 6 Day 1 (n= 14, 10)	0.0046 (± 0.00605)	99999 (± 99999)		
Cycle 7 Day 1 (n= 10, 7)	0.0058 (± 0.00496)	0.0044 (± 0.00692)		

Cycle 8 Day 1 (n= 10, 5)	0.0078 (± 0.00771)	99999 (± 99999)		
Cycle 9 Day 1 (n= 6, 5)	0.0067 (± 0.00480)	0.0068 (± 0.01329)		
Cycle 11 Day 1 (n= 1, 0)	99999 (± 99999)	0 (± 0)		
Cycle 13 Day 1 (n= 1, 0)	99999 (± 99999)	0 (± 0)		
Final Visit/Study Termination (n= 18, 23)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) Assessed as Per IIR

End point title	Duration of Response (DoR) Assessed as Per IIR

End point description:

DoR was based on IIR was the time from date of the first CR or PR until the date of first documentation of disease progression or date of death, if death occurred prior to disease progression, for the subjects who had BOR of CR or PR. Subjects without progressive disease or death were censored at the date of last adequate tumor assessment. DoR= End Date - Date of first CR or PR + 1. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

From date of the first CR or PR until the date of first documentation of disease progression or date of death, assessed up to data cutoff date 11 April 2011

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Months				
median (confidence interval 95%)	12.7 (8.8 to 99999)	99999 (5.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Assessed as Per IIR

End point title	Disease Control Rate (DCR) Assessed as Per IIR

End point description:

DCR was the percentage of the subjects who had BOR of CR, PR, and stable disease (SD) with the minimum duration of SD lasting greater than or equal to 7 weeks, based on assessments by IIR. DCR = CR+PR+SD greater than or equal to 7 weeks. ITT population. Subjects who were evaluable for this

given measure at a given time point were included for this assessment.

End point type	Secondary

End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, subject’s choice to stop study treatment, or up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	47		
Units: Percentage of subjects				
number (confidence interval 95%)	93.1 (83.3 to 98.1)	79.7 (67.2 to 89.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Assessed as Per IIR

End point title	Clinical Benefit Rate (CBR) Assessed as Per IIR

End point description:

CBR was the percentage of the subjects who had BOR of CR, PR, and SD with the minimum duration of SD lasting greater than or equal to 23 weeks, based on assessments by IIR. CBR = CR+PR+SD greater than or equal to 23 weeks. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment.

End point type	Secondary

End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, subject’s choice to stop study treatment, or up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	38		
Units: Percentage of subjects				
number (confidence interval 95%)	77.6 (64.7 to 87.5)	64.4 (50.9 to 76.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) Assessed as Per IIR

End point title	Time to Response (TTR) Assessed as Per IIR

End point description:

TTR was defined as "time from start of treatment to the time when a subject first achieves a response of PR/CR" based on assessments by IIR. TTR was only calculated for subjects with confirmed PR or CR. The Efficacy Evaluable Population included all subjects who received at least one dose of the study treatment, had a baseline and at least one posttreatment tumor response evaluation. Subjects who were evaluable for this given measure at a given time point were included for this assessment.

End point type	Secondary

End point timeframe:

From date of treatment start until date of first CR or PR, assessed up to data cutoff date 11 April 2011

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Months				
number (confidence interval 95%)	3.6 (1.8 to 3.7)	3.5 (1.9 to 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Assessed as Per IIR

End point title	Progression Free Survival (PFS) Assessed as Per IIR

End point description:

PFS was defined as the time from the date of treatment start until progressive disease or death from any cause in the absence of progressive disease. Disease progression was defined as at least a 20% increase in the sum of the longest diameter of target lesions (taking as reference the smallest sum on study), recorded since the treatment started or the appearance of 1 or more new lesions as assessed by IIR using RECIST 1.0. The duration of PFS was calculated as end date minus date of first drug plus 1, based on assessments by IIR. PFS was calculated using Kaplan-Meier estimate and presented with 2-sided 95% CI. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

From date of treatment start until date of progressive disease or death from any cause, assessed up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Months				
number (confidence interval 95%)	12.6 (9.9 to 16.1)	9.0 (7.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of treatment start until death from any cause. The duration of OS was calculated as 'end date minus date of first drug plus 1', based on assessments by IIR. Subjects without a reported death or those lost to follow-up were censored at their last known alive date at the database cutoff. OS was calculated using Kaplan-Meier estimate and presented with 2- sided 95% CI. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary

End point timeframe:

From date of treatment start until date of death from any cause, assessed up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Months				
number (confidence interval 95%)	27.7 (27.7 to 99999)	16.6 (16.4 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Non-Serious Adverse Events (AEs) and Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point title	Number of Subjects With Non-Serious Adverse Events (AEs) and Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point description:

Safety assessments consisted of monitoring and recording all AEs (serious and non-serious) and SAEs; concomitant medications, regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, New York Heart Association (NYHA) assessments, electrocardiograms (ECGs), echocardiograms; and performance of physical examinations. Safety population included all subjects who received at least 1 dose of study drug and had at least 1 posttreatment safety assessment.

End point type	Secondary

End point timeframe:

For each subject, from the first dose till 30 days after the last dose of study treatment (up to approximately 10 years 4 months)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Subjects				
number (not applicable)				
Non-Serious AEs	58	59		
SAEs	32	42		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each subject, from the first dose until 30 days after the last dose of study treatment (up to approximately 10 years 4 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	DTC Cohort

Reporting group description:

Subjects with radioiodine (131 I)-refractory/resistant DTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Reporting group title	MTC Cohort

Reporting group description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

Serious adverse events	DTC Cohort	MTC Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 58 (55.17%)	42 / 59 (71.19%)	
number of deaths (all causes)	44	37	
number of deaths resulting from adverse events	4	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngeal neoplasm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial rupture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 58 (3.45%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature menopause			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
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 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	3 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Stridor			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal fistula			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Echocardiogram abnormal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
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 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapyramidal disorder			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
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	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 58 (1.72%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder enlargement			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abscess neck			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (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	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	5 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcitoninaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DTC Cohort	MTC Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 58 (100.00%)	59 / 59 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	3	1	
Hypertension			
subjects affected / exposed	45 / 58 (77.59%)	31 / 59 (52.54%)	
occurrences (all)	108	74	
Hypotension			
subjects affected / exposed	14 / 58 (24.14%)	10 / 59 (16.95%)	
occurrences (all)	19	19	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 58 (24.14%)	6 / 59 (10.17%)	
occurrences (all)	36	32	
Chest discomfort			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Chills			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	4	5	
Fatigue			
subjects affected / exposed	35 / 58 (60.34%)	33 / 59 (55.93%)	
occurrences (all)	97	84	
Influenza like illness			
subjects affected / exposed	4 / 58 (6.90%)	6 / 59 (10.17%)	
occurrences (all)	4	8	
Local swelling			

subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Malaise			
subjects affected / exposed	0 / 58 (0.00%)	5 / 59 (8.47%)	
occurrences (all)	0	6	
Mucosal inflammation			
subjects affected / exposed	6 / 58 (10.34%)	7 / 59 (11.86%)	
occurrences (all)	7	8	
Oedema peripheral			
subjects affected / exposed	14 / 58 (24.14%)	8 / 59 (13.56%)	
occurrences (all)	20	8	
Pain			
subjects affected / exposed	6 / 58 (10.34%)	3 / 59 (5.08%)	
occurrences (all)	6	3	
Peripheral swelling			
subjects affected / exposed	5 / 58 (8.62%)	4 / 59 (6.78%)	
occurrences (all)	11	4	
Pyrexia			
subjects affected / exposed	15 / 58 (25.86%)	12 / 59 (20.34%)	
occurrences (all)	21	17	
Temperature intolerance			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	4	4	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 58 (48.28%)	24 / 59 (40.68%)	
occurrences (all)	46	38	
Dysphonia			
subjects affected / exposed	25 / 58 (43.10%)	20 / 59 (33.90%)	
occurrences (all)	39	38	
Dyspnoea			

subjects affected / exposed	20 / 58 (34.48%)	16 / 59 (27.12%)	
occurrences (all)	32	25	
Epistaxis			
subjects affected / exposed	18 / 58 (31.03%)	13 / 59 (22.03%)	
occurrences (all)	28	21	
Haemoptysis			
subjects affected / exposed	6 / 58 (10.34%)	8 / 59 (13.56%)	
occurrences (all)	10	13	
Nasal congestion			
subjects affected / exposed	4 / 58 (6.90%)	2 / 59 (3.39%)	
occurrences (all)	6	2	
Nasal dryness			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Oropharyngeal pain			
subjects affected / exposed	16 / 58 (27.59%)	13 / 59 (22.03%)	
occurrences (all)	35	25	
Pleural effusion			
subjects affected / exposed	5 / 58 (8.62%)	4 / 59 (6.78%)	
occurrences (all)	9	4	
Productive cough			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences (all)	6	3	
Rhinorrhoea			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 58 (10.34%)	8 / 59 (13.56%)	
occurrences (all)	7	9	
Confusional state			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Depression			
subjects affected / exposed	11 / 58 (18.97%)	5 / 59 (8.47%)	
occurrences (all)	11	6	

Insomnia			
subjects affected / exposed	13 / 58 (22.41%)	7 / 59 (11.86%)	
occurrences (all)	14	9	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	6 / 58 (10.34%)	5 / 59 (8.47%)	
occurrences (all)	6	5	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 58 (12.07%)	9 / 59 (15.25%)	
occurrences (all)	17	21	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 58 (15.52%)	9 / 59 (15.25%)	
occurrences (all)	15	18	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	5	12	
Blood bilirubin increased			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 58 (6.90%)	2 / 59 (3.39%)	
occurrences (all)	6	3	
Blood creatinine increased			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	4	11	
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	3	1	
Blood pressure increased			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	9	4	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	

Blood thyroid stimulating hormone increased			
subjects affected / exposed	4 / 58 (6.90%)	13 / 59 (22.03%)	
occurrences (all)	4	16	
Blood triglycerides increased			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	3	5	
Blood urea increased			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	9	2	
Blood urine present			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	5	7	
Haemoglobin decreased			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	5	3	
Platelet count decreased			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	7	3	
Prothrombin time prolonged			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Weight decreased			
subjects affected / exposed	39 / 58 (67.24%)	29 / 59 (49.15%)	
occurrences (all)	125	81	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	7	
Fall			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	5	
Thermal burn			

subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Bradycardia			
subjects affected / exposed	5 / 58 (8.62%)	0 / 59 (0.00%)	
occurrences (all)	6	0	
Sinus tachycardia			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Tachycardia			
subjects affected / exposed	7 / 58 (12.07%)	7 / 59 (11.86%)	
occurrences (all)	7	9	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Dizziness			
subjects affected / exposed	10 / 58 (17.24%)	13 / 59 (22.03%)	
occurrences (all)	14	15	
Dysgeusia			
subjects affected / exposed	12 / 58 (20.69%)	9 / 59 (15.25%)	
occurrences (all)	14	13	
Headache			
subjects affected / exposed	27 / 58 (46.55%)	27 / 59 (45.76%)	
occurrences (all)	49	59	
Hyperaesthesia			
subjects affected / exposed	1 / 58 (1.72%)	11 / 59 (18.64%)	
occurrences (all)	1	15	
Hypoaesthesia			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	5	4	
Paraesthesia			

subjects affected / exposed	7 / 58 (12.07%)	1 / 59 (1.69%)	
occurrences (all)	8	1	
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	8	4	
Sinus headache			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	3	2	
Somnolence			
subjects affected / exposed	0 / 58 (0.00%)	5 / 59 (8.47%)	
occurrences (all)	0	8	
Tremor			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	9	
Leukopenia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	4	2	
Lymphadenopathy			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Lymphopenia			
subjects affected / exposed	2 / 58 (3.45%)	6 / 59 (10.17%)	
occurrences (all)	3	6	
Neutropenia			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	7	3	
Thrombocytopenia			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	3	8	
Ear and labyrinth disorders			
Ear discomfort			

subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	4	
Ear pain			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	5	0	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Lacrimation increased			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	
occurrences (all)	4	1	
Vision blurred			
subjects affected / exposed	4 / 58 (6.90%)	2 / 59 (3.39%)	
occurrences (all)	4	2	
Visual impairment			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 58 (13.79%)	2 / 59 (3.39%)	
occurrences (all)	12	2	
Abdominal pain			
subjects affected / exposed	20 / 58 (34.48%)	19 / 59 (32.20%)	
occurrences (all)	31	38	
Abdominal pain lower			
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences (all)	2	5	
Abdominal pain upper			
subjects affected / exposed	18 / 58 (31.03%)	18 / 59 (30.51%)	
occurrences (all)	33	28	
Cheilitis			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	5	3	
Constipation			

subjects affected / exposed	16 / 58 (27.59%)	17 / 59 (28.81%)	
occurrences (all)	23	37	
Diarrhoea			
subjects affected / exposed	40 / 58 (68.97%)	45 / 59 (76.27%)	
occurrences (all)	146	242	
Dry mouth			
subjects affected / exposed	21 / 58 (36.21%)	10 / 59 (16.95%)	
occurrences (all)	25	11	
Dyspepsia			
subjects affected / exposed	6 / 58 (10.34%)	8 / 59 (13.56%)	
occurrences (all)	8	10	
Dysphagia			
subjects affected / exposed	14 / 58 (24.14%)	12 / 59 (20.34%)	
occurrences (all)	17	16	
Faeces pale			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	6	0	
Flatulence			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	5	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 58 (8.62%)	7 / 59 (11.86%)	
occurrences (all)	9	11	
Gingival bleeding			
subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	7	
Gingival pain			
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)	
occurrences (all)	1	7	
Glossitis			
subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)	
occurrences (all)	5	1	
Glossodynia			
subjects affected / exposed	9 / 58 (15.52%)	12 / 59 (20.34%)	
occurrences (all)	14	17	
Haematochezia			

subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences (all)	2	4	
Haemorrhoids			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	5	2	
Mouth ulceration			
subjects affected / exposed	3 / 58 (5.17%)	5 / 59 (8.47%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	30 / 58 (51.72%)	30 / 59 (50.85%)	
occurrences (all)	70	82	
Oesophagitis			
subjects affected / exposed	4 / 58 (6.90%)	0 / 59 (0.00%)	
occurrences (all)	5	0	
Oral discomfort			
subjects affected / exposed	3 / 58 (5.17%)	8 / 59 (13.56%)	
occurrences (all)	3	10	
Oral pain			
subjects affected / exposed	7 / 58 (12.07%)	8 / 59 (13.56%)	
occurrences (all)	14	11	
Stomatitis			
subjects affected / exposed	19 / 58 (32.76%)	15 / 59 (25.42%)	
occurrences (all)	55	22	
Tongue disorder			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Toothache			
subjects affected / exposed	5 / 58 (8.62%)	6 / 59 (10.17%)	
occurrences (all)	5	7	
Vomiting			
subjects affected / exposed	23 / 58 (39.66%)	25 / 59 (42.37%)	
occurrences (all)	83	91	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 58 (12.07%)	7 / 59 (11.86%)	
occurrences (all)	7	7	

Blister				
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)		
occurrences (all)	2	6		
Dermatitis				
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)		
occurrences (all)	2	3		
Dermatitis acneiform				
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)		
occurrences (all)	1	3		
Dermatitis allergic				
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)		
occurrences (all)	4	2		
Dry skin				
subjects affected / exposed	10 / 58 (17.24%)	11 / 59 (18.64%)		
occurrences (all)	14	17		
Erythema				
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)		
occurrences (all)	4	4		
Exfoliative rash				
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)		
occurrences (all)	2	8		
Hair texture abnormal				
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)		
occurrences (all)	3	0		
Hyperhidrosis				
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)		
occurrences (all)	2	3		
Hyperkeratosis				
subjects affected / exposed	4 / 58 (6.90%)	7 / 59 (11.86%)		
occurrences (all)	4	10		
Night sweats				
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)		
occurrences (all)	0	3		
Palmar-plantar erythrodysaesthesia syndrome				

subjects affected / exposed	15 / 58 (25.86%)	15 / 59 (25.42%)	
occurrences (all)	37	45	
Pruritus			
subjects affected / exposed	5 / 58 (8.62%)	5 / 59 (8.47%)	
occurrences (all)	7	6	
Rash			
subjects affected / exposed	10 / 58 (17.24%)	16 / 59 (27.12%)	
occurrences (all)	12	28	
Rash macular			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Rash papular			
subjects affected / exposed	3 / 58 (5.17%)	6 / 59 (10.17%)	
occurrences (all)	3	7	
Rash pruritic			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	4	2	
Skin exfoliation			
subjects affected / exposed	2 / 58 (3.45%)	6 / 59 (10.17%)	
occurrences (all)	5	16	
Skin fissures			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	6	1	
Skin induration			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	6	6	
Skin lesion			
subjects affected / exposed	7 / 58 (12.07%)	4 / 59 (6.78%)	
occurrences (all)	11	6	
Skin ulcer			
subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)	
occurrences (all)	5	2	
Swelling face			
subjects affected / exposed	0 / 58 (0.00%)	5 / 59 (8.47%)	
occurrences (all)	0	7	
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Haematuria			
subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)	
occurrences (all)	7	2	
Pollakiuria			
subjects affected / exposed	4 / 58 (6.90%)	2 / 59 (3.39%)	
occurrences (all)	4	3	
Proteinuria			
subjects affected / exposed	41 / 58 (70.69%)	38 / 59 (64.41%)	
occurrences (all)	195	160	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Hypothyroidism			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 58 (37.93%)	21 / 59 (35.59%)	
occurrences (all)	51	51	
Arthritis			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Back pain			
subjects affected / exposed	23 / 58 (39.66%)	14 / 59 (23.73%)	
occurrences (all)	34	31	
Bone pain			
subjects affected / exposed	5 / 58 (8.62%)	3 / 59 (5.08%)	
occurrences (all)	5	15	
Joint stiffness			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	3	4	
Joint swelling			

subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Muscle spasms			
subjects affected / exposed	13 / 58 (22.41%)	7 / 59 (11.86%)	
occurrences (all)	27	11	
Muscle tightness			
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)	
occurrences (all)	1	5	
Muscular weakness			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	6	5	
Musculoskeletal chest pain			
subjects affected / exposed	14 / 58 (24.14%)	14 / 59 (23.73%)	
occurrences (all)	14	19	
Musculoskeletal pain			
subjects affected / exposed	19 / 58 (32.76%)	17 / 59 (28.81%)	
occurrences (all)	33	24	
Musculoskeletal stiffness			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	4	
Myalgia			
subjects affected / exposed	14 / 58 (24.14%)	14 / 59 (23.73%)	
occurrences (all)	29	27	
Neck pain			
subjects affected / exposed	8 / 58 (13.79%)	9 / 59 (15.25%)	
occurrences (all)	11	10	
Pain in extremity			
subjects affected / exposed	19 / 58 (32.76%)	17 / 59 (28.81%)	
occurrences (all)	46	43	
Pain in jaw			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	2	12	
Periarthritis			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Flank pain			

subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	4	5	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	2	5	
Gastroenteritis viral			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences (all)	5	5	
Gingivitis			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	7	
Influenza			
subjects affected / exposed	6 / 58 (10.34%)	7 / 59 (11.86%)	
occurrences (all)	10	9	
Laryngitis			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Localised infection			
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences (all)	2	8	
Lower respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	5 / 59 (8.47%)	
occurrences (all)	0	10	
Nasopharyngitis			
subjects affected / exposed	2 / 58 (3.45%)	7 / 59 (11.86%)	
occurrences (all)	3	21	
Oral candidiasis			
subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	5	
Pharyngitis			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	5	7	
Pneumonia			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	
occurrences (all)	6	1	

Rash pustular			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Rhinitis			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Sinusitis			
subjects affected / exposed	3 / 58 (5.17%)	6 / 59 (10.17%)	
occurrences (all)	5	12	
Tooth abscess			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	4	5	
Upper respiratory tract infection			
subjects affected / exposed	12 / 58 (20.69%)	12 / 59 (20.34%)	
occurrences (all)	13	19	
Urinary tract infection			
subjects affected / exposed	11 / 58 (18.97%)	8 / 59 (13.56%)	
occurrences (all)	15	17	
Vaginal infection			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	3	1	
Viral infection			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Gastroenteritis			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	2	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 58 (55.17%)	32 / 59 (54.24%)	
occurrences (all)	61	74	
Dehydration			
subjects affected / exposed	9 / 58 (15.52%)	6 / 59 (10.17%)	
occurrences (all)	10	10	
Dyslipidaemia			

subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Hypercalcaemia			
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)	
occurrences (all)	1	5	
Hypercholesterolaemia			
subjects affected / exposed	6 / 58 (10.34%)	2 / 59 (3.39%)	
occurrences (all)	15	5	
Hyperglycaemia			
subjects affected / exposed	4 / 58 (6.90%)	6 / 59 (10.17%)	
occurrences (all)	13	9	
Hyperkalaemia			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Hypertriglyceridaemia			
subjects affected / exposed	6 / 58 (10.34%)	2 / 59 (3.39%)	
occurrences (all)	22	2	
Hypoalbuminaemia			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	5	
Hypocalcaemia			
subjects affected / exposed	9 / 58 (15.52%)	12 / 59 (20.34%)	
occurrences (all)	21	20	
Hypoglycaemia			
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences (all)	2	4	
Hypokalaemia			
subjects affected / exposed	6 / 58 (10.34%)	7 / 59 (11.86%)	
occurrences (all)	8	12	
Hypomagnesaemia			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Hyponatraemia			
subjects affected / exposed	3 / 58 (5.17%)	5 / 59 (8.47%)	
occurrences (all)	3	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2009	Amendment 01: The protocol was amended to remove the dose limiting toxicity component of study and changed to once daily dosing of 24 mg instead of twice daily 10 mg dosing, change the study design to Simon's optimal two-stage design, which would have allowed for early termination of the study if the response was not sufficient, add simplified electrocardiogram (ECG) monitoring scheme, increased the timing of disease progression window to 12 months from 6 months for inclusion criteria, include proteinuria as a toxicity.
12 April 2010	Amendment 02: The protocol was amended to clarify that subjects with classical papillary thyroid cancer and minimally or widely invasive follicular thyroid cancer could have been included in the subject population, remove renal function with serum creatinine greater than (>) 1.5 upper limit normal (ULN) as an exclusion criteria, exclude subjects with greater than or equal to (>=) 1 gram (g) per (/)24 hour proteinuria, include a section on reporting overdose of study drug and include the reporting of significant treatment-emergent laboratory abnormalities as adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported