

**Clinical trial results:****Sunitinib treatment of renal adjuvant cancer (S TRAC): A randomized double blind phase 3 study of adjuvant sunitinib vs. placebo in subjects at high risk of recurrent renal cell carcinoma (RCC)****Summary**

EudraCT number	2006-004024-37
Trial protocol	FR GB CZ DE GR AT IT IE SE PL SK DK ES
Global end of trial date	30 August 2017

Results information

Result version number	v2
This version publication date	10 August 2018
First version publication date	23 March 2017
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	A6181109
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00375674
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, 10017
Public contact	Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 June 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate an improvement in disease-free survival (DFS) in subjects with RCC at high risk of disease recurrence after nephrectomy (per modified UISS criteria) randomly assigned to adjuvant sunitinib 50 mg once daily (QD) on Schedule 4/2 (4 weeks on, 2 weeks off treatment) for 1 year (9 cycles) versus placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	China: 20
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	France: 99
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Ireland: 15
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Slovakia: 33
Country: Number of subjects enrolled	Spain: 41

Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	United Kingdom: 43
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	615
EEA total number of subjects	463

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)	457
From 65 to 84 years	158
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 674 enrolled subjects (615 in global cohort and 59 in china cohort), the results presented refers to the study conducted on 615 (intent-to-treat population) in 21 countries and were randomized to sunitinib and placebo for 9 cycles (1 cycle=42 days).

Pre-assignment

Screening details:

Screening: From Week 0 (nephrectomy surgery) to Week 11; in this period, echocardiogram/multi-gated acquisition, post-surgery imaging, histopathology, physical examination, laboratory tests, electrocardiogram and concomitant treatment were assessed. Randomization occurred not before 3 weeks post-nephrectomy & not after 12 weeks post-nephrectomy

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, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Sunitinib

Arm description:

Subjects received Sunitinib on 9 6-week cycles on 4/2 dosing schedule: 4 weeks on, 2 weeks off.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sunitinib was self administered orally at the same time each day (eg, morning or evening), without regard to meals, beginning on Cycle 1 Day 1 of study treatment. Subjects experiencing toxicity were managed by treatment interruption or dose reduction to 37.5 milligram (mg) four times a day (QD), and/or permanent discontinuation from study treatment.

Arm title	Placebo
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Arm description:

Subjects received Placebo on 9 6-week cycles with 4/2 dosing schedule: 4 weeks on, 2 weeks off.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was self administered orally at the same time each day (eg, morning or evening), without regard to meals, beginning on Cycle 1 Day 1 of study treatment. Subjects experiencing toxicity were managed by treatment interruption or dose reduction to 37.5 mg QD, and/or permanent discontinuation from study treatment.

Number of subjects in period 1	Sunitinib	Placebo
Started	309	306
Intent-to-Treat population	309	306
As-Treated population	306	304
Completed	165	165
Not completed	144	141
Death	67	76
Not specified	26	18
Subject refused further follow-up	31	30
Lost to follow-up	17	15
Enrolled but not treated	3	2

Baseline characteristics

Reporting groups

Reporting group title	Sunitinib
Reporting group description:	
Subjects received Sunitinib on 9 6-week cycles on 4/2 dosing schedule: 4 weeks on, 2 weeks off.	
Reporting group title	Placebo
Reporting group description:	
Subjects received Placebo on 9 6-week cycles with 4/2 dosing schedule: 4 weeks on, 2 weeks off.	

Reporting group values	Sunitinib	Placebo	Total
Number of subjects	309	306	615
Age categorical			
Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	233	224	457
>=65 years	76	82	158
Age continuous			
Units: years			
arithmetic mean	56.8	57.9	
standard deviation	± 10.6	± 10.6	-
Gender categorical			
Units: Subjects			
Female	87	77	164
Male	222	229	451

End points

End points reporting groups

Reporting group title	Sunitinib
Reporting group description: Subjects received Sunitinib on 9 6-week cycles on 4/2 dosing schedule: 4 weeks on, 2 weeks off.	
Reporting group title	Placebo
Reporting group description: Subjects received Placebo on 9 6-week cycles with 4/2 dosing schedule: 4 weeks on, 2 weeks off.	

Primary: Disease-free survival (DFS)- Assessed by Blinded Independent Central Review

End point title	Disease-free survival (DFS)- Assessed by Blinded Independent Central Review
End point description: DFS: the time interval from date of randomization to first date of recurrence or occurrence of a secondary malignancy or death. Recurrence: Relapse of primary tumor in-situ or at metastatic sites. Subjects were followed with tumor imaging for recurrence or occurrence of a secondary malignancy for remainder of follow-up period unless subject had withdrawn consent. According to statistical analysis plan there are two cohorts: 1.Global Cohort: primary analysis of DFS was performed approximately 5 years after last subject in Global Cohort was randomized; 2. China Cohort: primary analysis of DFS was performed approximately 3 years after last subject in China Cohort was randomized. ITT population: all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. Here, 99999=Upper limit of 95% CI of median DFS was not reached.	
End point type	Primary
End point timeframe: Every 12 weeks during the first 3 years and every 6 months after that unless the subject had withdrawn consent. Performed 5 years after LSLV or when approximately 258 events survival status, whichever was later	

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Years				
number (confidence interval 95%)				
DFS- Assessed by BICR	6.8 (5.8 to 99999)	5.6 (3.8 to 6.6)		

Statistical analyses

Statistical analysis title	DFS- Assessed by BICR
Statistical analysis description: Based on the Cox Proportional hazards model stratified by UISS High-Risk Group.	
Comparison groups	Placebo v Sunitinib

Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Cox Proportional hazards model
Parameter estimate	Cox proportional hazard
Point estimate	0.761
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.594
upper limit	0.975

Secondary: DFS- Assessed by the Investigator [Stratified by University of California Los Angeles Integrated Staging System (UISS) High Risk Group-Intent to Treat Population]

End point title	DFS- Assessed by the Investigator [Stratified by University of California Los Angeles Integrated Staging System (UISS) High Risk Group-Intent to Treat Population]
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End point description:

DFS: time interval from date of randomization to first date of recurrence or occurrence of a secondary malignancy or death. Recurrence: relapse of primary tumor in-situ or at metastatic sites Subjects were followed with tumor imaging for recurrence or occurrence of a secondary malignancy for the remainder of the follow-up period unless the patient had withdrawn consent. According to the statistical analysis plan there are two cohorts: 1.Global Cohort: primary analysis of DFS was performed approximately 5 years after last subject in the Global Cohort is randomized; 2. China Cohort: primary analysis of DFS was performed approximately 3 years after the last subject in China Cohort was randomized. ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

End point type	Secondary
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End point timeframe:

Every 12 weeks during the first 3 years and every 6 months after that unless the subject had withdrawn consent. Performed 5 years after LSLV or when approximately 258 events survival status, whichever was later

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Years				
number (confidence interval 95%)				
DFS- Assessed by the Investigator	6.5 (4.7 to 7.0)	4.5 (3.8 to 5.9)		

Statistical analyses

Statistical analysis title	DFS- Assessed by the Investigator
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Statistical analysis description:

Based on the Cox Proportional hazards model stratified by UISS High-Risk Group.

Comparison groups	Sunitinib v Placebo
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.077
Method	Cox Proportional hazards model
Parameter estimate	Cox proportional hazard
Point estimate	0.811
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.643
upper limit	1.023

Secondary: Overall survival (OS)- (Stratified by UISS High Risk Group-Intent to Treat Population)

End point title	Overall survival (OS)- (Stratified by UISS High Risk Group-Intent to Treat Population)
End point description:	
OS was defined as the time from the date of randomization to the date of death due to any cause. ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.. Here, 99999 refers to data was not estimable due to small number of subjects with an event.	
End point type	Secondary
End point timeframe:	
Every 12 weeks until the time for final analysis (up to data cut-off date: 30 April 2017; maximum exposure:14.9 months)	

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Years				
median (confidence interval 95%)				
Overall survival	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	OS- Stratified by UISS High Risk Group
Statistical analysis description:	
Hazard ratio was based on the Cox Proportional hazards model stratified by UISS High-Risk Group.	
Comparison groups	Sunitinib v Placebo

Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.661
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.929
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.289

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) by Severity

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) by Severity
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End point description:

TEAEs are all AEs occurred, for the first time, on or after the first day of study treatment. AEs started before the first dose of study treatment but increased in severity over the baseline will also be considered TEAEs. Subjects were followed for AEs from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. The treatment was administered to the subjects from cycle1/day 1 up to 9 cycles or until relapse, secondary malignancy, death or withdraw for other reasons such as toxicity or withdraw of consent. The As-Treated (AT) population included all subjects who received at least 1 dose of study drug with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/ compliance and safety.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1 & Day 28); subsequent cycles (Day 1); end of treatment/withdrawal and 28 days post treatment, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306	304		
Units: Number of subjects				
Subjects With AEs	305	270		
Subjects With Serious Adverse Events (SAEs)	67	52		
Subjects With Grade 3 or Grade 4 AEs	189	61		
Subjects With Grade 5 AEs	5	5		
Subjects Discontinued Due to AEs	86	16		
Subjects With Dose Reduced Due to AEs	106	6		
Subjects With Temporary Discontinuation Due to AEs	141	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Duration of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Terms (All Causalities, All Cycles)

End point title	Summary of Duration of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Terms (All Causalities, All Cycles)
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End point description:

TEAEs are all AEs occurred, for first time, on or after first day of study treatment. AEs started before first dose of study treatment but increased in severity over baseline will also be considered TEAEs. Subjects were followed for AEs from first day of study treatment until at least 28 days after last on-study treatment administration, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. The treatment was administered to subjects from cycle1/day 1 up to 9 cycles or until relapse, secondary malignancy, death or withdraw for other reasons such as toxicity or withdraw of consent. The AT population included all subjects who received at least 1 dose of study drug with treatment assignments designated. Here "n" signifies the number of subjects analyzed at each time point. Here 99999 refers that standard deviation cannot be calculated due to single subject.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1 & Day 28); subsequent cycles (Day 1); end of treatment/withdrawal and 28 days post treatment, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306	304		
Units: Weeks				
arithmetic mean (standard deviation)				
Benign Neoplasm of Thyroid Gland, (n=0,1)	99999 (± 99999)	35.1 (± 9999)		
Goitre, (n=0,2)	99999 (± 99999)	305.6 (± 97.08)		
Hyperthyroidism, (n=12,2)	23.2 (± 25.95)	110.8 (± 146.57)		
Hypothyroidism, (n=56,4)	46.9 (± 75.3)	58 (± 62.06)		
Papillary Thyroid Cancer, (n=0,1)	99999 (± 99999)	22.1 (± 9999)		
Thyroid Disorder, (n=1,0)	19 (± 9999)	99999 (± 99999)		
Thyroid Mass, (n=0,1)	99999 (± 99999)	20.4 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs)- European Organization for Research and Treatment of Cancer (EORTC) QLQ C30: Observed Means in Global Health Status / Quality of Life Scale Scores

End point title	Patient-reported outcomes (PROs)- European Organization for Research and Treatment of Cancer (EORTC) QLQ C30: Observed Means in Global Health Status / Quality of Life Scale Scores
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End point description:

PROs assessed health-related quality of life (QoL) by using the EORTC QLQ-C30, which was a 30-item questionnaire with global QoL scale, 5 multi-item functional scales (physical, role, emotional, cognitive, & social functioning), 3 multi-item symptom scales (fatigue, nausea/vomiting, & pain), and 6 single item symptom scales for other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, & the financial impact of cancer). The questionnaire includes 28 items with 4-point Likert type responses from "not at all" to "very much" to assess functioning & symptoms; 2 items with 7-point Likert scales for global health & overall QoL. ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or a different drug from that to which they were randomized. Here "n" signifies the number of subjects analyzed at each time point.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1); subsequent cycles (Day 1) and end of treatment/withdrawal (ie, up to 1 year)

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Scores on scale				
arithmetic mean (standard error)				
Cycle 1 (Baseline), (n=292,288)	74.83 (± 1.044)	75.61 (± 1.044)		
Cycle 2, (n=260,274)	69.71 (± 1.289)	75.49 (± 1.097)		
Cycle 3, (n=241,265)	69.67 (± 1.278)	74.09 (± 1.142)		
Cycle 4, (n=227,249)	66.52 (± 1.307)	74.93 (± 1.109)		
Cycle 5, (n=219,234)	68.34 (± 1.34)	74.61 (± 1.179)		
Cycle 6, (n=210,231)	66.27 (± 1.396)	75.69 (± 1.172)		
Cycle 7, (n=200,220)	67.42 (± 1.447)	73.98 (± 1.222)		
Cycle 8, (n=185,212)	68.33 (± 1.376)	74.49 (± 1.26)		
Cycle 9, (n=177,203)	68.31 (± 1.556)	74.06 (± 1.338)		
End of treatment (EOT), (n=250,250)	64.43 (± 1.367)	73.37 (± 1.264)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROs- EORTC QLQ C30: Functional Scale Scores Between Treatment Comparison

End point title	PROs- EORTC QLQ C30: Functional Scale Scores Between Treatment Comparison
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End point description:

PROs assessed health-related QoL by using the EORTC QLQ-C30, which was a 30-item questionnaire with global QoL scale & 5 multi-item functional scales (physical, role, emotional, cognitive, & social functioning). The questionnaire includes 28 items with 4-point Likert type responses from "not at all" to "very much" to assess functioning; 2 items with 7-point Likert scales for global health & overall QoL. All responses were converted to a 0 to 100 scale using a standard scoring algorithm, higher scores represented better level for functioning/QoL. ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1); subsequent cycles (Day 1) and end of treatment/withdrawal (ie, up to 1 year)

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Scores on scale				
arithmetic mean (confidence interval 95%)				
Physical	83.54 (82.4 to 84.68)	87.53 (86.42 to 88.64)		
Role	78.94 (77.14 to 80.74)	85.46 (83.7 to 87.23)		
Emotional	80.92 (79.58 to 82.27)	82.97 (81.66 to 84.29)		
Cognitive	85.5 (84.17 to 86.83)	87.43 (86.13 to 88.73)		
Social	80.62 (79.04 to 82.21)	87.99 (86.44 to 89.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROs- EORTC QLQ-C30: Symptom Scale Scores Between Treatment Comparison

End point title	PROs- EORTC QLQ-C30: Symptom Scale Scores Between Treatment Comparison
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End point description:

PROs assessed health-related QoL by using the EORTC QLQ-C30, which was a 30-item questionnaire with global QoL scale & 5 multi-item functional scales (physical, role, emotional, cognitive, & social functioning). The questionnaire includes 28 items with 4-point Likert type responses from "not at all" to "very much" to assess functioning; 2 items with 7-point Likert scales for global health & overall QoL. All responses were converted to a 0 to 100 scale using a standard scoring algorithm, higher scores represented better level for functioning/QoL. ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether

subjects received study drug or received a different drug from that to which they were randomized.

End point type	Secondary
End point timeframe:	
Cycle 1(Day 1); subsequent cycles (Day 1) and end of treatment/withdrawal (ie, up to 1 year)	

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Scores on scale				
arithmetic mean (confidence interval 95%)				
Fatigue	29.94 (28.33 to 31.56)	21.74 (20.16 to 23.31)		
Nausea and Vomiting	7.35 (6.38 to 8.33)	3.46 (2.51 to 4.41)		
Pain	21.81 (20.1 to 23.52)	16.63 (14.96 to 18.3)		
Dyspnoea	14.97 (13.38 to 16.57)	11.89 (10.33 to 13.45)		
Insomnia	22.22 (20.26 to 24.19)	20.73 (18.81 to 22.65)		
Appetite Loss	14.66 (13.12 to 16.21)	4.62 (3.11 to 6.13)		
Constipation	11.24 (9.66 to 12.82)	9.83 (8.29 to 11.37)		
Diarrhoea	19.25 (17.54 to 20.95)	7.25 (5.59 to 8.91)		
Financial Difficulties	15.12 (13.42 to 16.82)	13.92 (12.26 to 15.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROs- EuroQoL EQ-5D Observed Means– Intent to Treat Population

End point title	PROs- EuroQoL EQ-5D Observed Means– Intent to Treat Population
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End point description:

PROs assessed health-related QoL by EuroQoL Group health status questionnaire (EQ-5D), which was a brief self-administered, validated instrument with 2 parts. In this endpoint, the first part with 5 descriptors of current health state (mobility, self-care, usual activities, pain/discomfort, & anxiety/depression) was used; a subject was asked to rate each state on a 3-level scale (1=no problem, 2=some problem, 3=extreme problem); higher levels indicated greater severity/impairment. The published weights allowed the creation of a single summary score called the EQ-5D index, which ranged from -0.594 to 1; low scores represented a higher level of dysfunction & 1 as perfect health. ITT population included all subject who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subject received study drug or a different drug from that to which they were randomized. Here "n" signifies the number of subjects analyzed at each time point.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1); subsequent cycles (Day 1) and end of treatment/withdrawal (ie, up to 1 year)

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Mean				
arithmetic mean (standard error)				
Cycle 1 (Baseline), (n=293,287)	0.84 (± 0.011)	0.83 (± 0.011)		
Cycle 2, (n=255,271)	0.83 (± 0.011)	0.84 (± 0.011)		
Cycle 3, (n=235,267)	0.8 (± 0.013)	0.82 (± 0.012)		
Cycle 4, (n=231,245)	0.77 (± 0.014)	0.84 (± 0.011)		
Cycle 5, (n=218,230)	0.77 (± 0.016)	0.084 (± 0.13)		
Cycle 6, (n=211,234)	0.78 (± 0.016)	0.85 (± 0.012)		
Cycle 7, (n=199,216)	0.77 (± 0.016)	0.83 (± 0.014)		
Cycle 8, (n=185,207)	0.8 (± 0.015)	0.84 (± 0.013)		
Cycle 9, (n=174,202)	0.081 (± 0.015)	0.85 (± 0.013)		
EOT, (n=250,245)	0.75 (± 0.017)	0.83 (± 0.015)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROs- EuroQol European Quality of Life Questionnaire Variable Analogue Scale (EQ-VAS) Observed Means

End point title	PROs- EuroQol European Quality of Life Questionnaire Variable Analogue Scale (EQ-VAS) Observed Means
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End point description:

PROs assessed health-related QoL by the EuroQoL Group health status questionnaire (EQ-5D), which was a brief self-administered, validated instrument with 2 parts. The first part assessed the current health state. In this endpoint, the second part was applied to assess the general health status by using visual analog scale (EQ-5D VAS) which measured subject's self-rated health status on a scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or a different drug from that to which they were randomized. Here "n" signifies the number of subjects analyzed at each time point.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1); subsequent cycles (Day 1) and end of treatment/withdrawal (ie, up to 1 year)

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Mean				
arithmetic mean (standard error)				
Cycle 1 (Baseline), (n= 293,287)	77.31 (± 0.999)	75.67 (± 1.08)		

Cycle 2, (n= 261,268)	74.39 (± 1.188)	76.99 (± 1.08)		
Cycle 3, (n= 234,261)	74.2 (± 1.093)	76.85 (± 1.122)		
Cycle 4, (n= 231,246)	74.14 (± 1.118)	77.34 (± 1.115)		
Cycle 5, (n= 218,233)	73.3 (± 1.22)	77.56 (± 1.212)		
Cycle 6, (n= 211,232)	73.51 (± 1.25)	78.61 (± 1.13)		
Cycle 7, (n= 199,218)	72.27 (± 1.267)	77.49 (± 1.18)		
Cycle 8, (n= 186,209)	73.96 (± 1.226)	77.65 (± 1.213)		
Cycle 9, (n= 174,203)	72.93 (± 1.424)	79.02 (± 1.168)		
EOT, (n= 251,246)	71.79 (± 1.139)	76.93 (± 1.283)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Tolerability Symptoms

End point title	Number of Subjects With Tolerability Symptoms
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End point description:

Subjects were followed for AEs from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. The treatment was administered to the subjects from cycle1/day 1 up to 9 cycles or until relapse, secondary malignancy, death or withdraw for other reasons such as toxicity or withdraw of consent. This table provides the summary of discontinuations de to adverse events. Subjects were counted only once in each row. ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

End point type	Secondary
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End point timeframe:

Cycle 1(Day 1 & Day 28); subsequent cycles (Day 1); end of treatment/withdrawal and 28 days post treatment, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Number of subjects				
number (not applicable)				
Palmar-plantar erythrodysesthesia syndrome	13	0		
Hypertension	6	0		
Asthenia	4	0		
Fatigue	3	1		
Pulmonary embolism	3	1		
Gastrooesophageal reflux disease	3	0		

Ejection fraction decreased	2	1		
Left ventricular dysfunction	2	1		
Acute myocardial infarction	2	0		
Blood creatinine increased	2	0		
Dehydration	2	0		
Dyspepsia	2	0		
Proteinuria	2	0		
Thrombocytopenia	2	0		
Upper gastrointestinal haemorrhage	2	0		
Vomiting	2	0		
Electrocardiogram QT prolonged	1	1		
Lethargy	1	1		
Transient ischaemic attack	1	1		
Depression	0	2		
Abdominal pain	1	0		
Abdominal pain upper	1	0		
Acute kidney injury	1	0		
Ageusia	1	0		
Alanine aminotransferase increased	1	0		
Anal inflammation	1	0		
Anal pruritus	1	0		
Aspartate aminotransferase increased	1	0		
Atrial fibrillation	1	0		
Atrial flutter	1	0		
Diarrhoea	1	0		
Disease progression	1	0		
Dysgeusia	1	0		
Electrocardiogram ST segment abnormal	1	0		
Embolism venous	1	0		
Eyelid oedema	1	0		
Gastritis haemorrhagic	1	0		
Glossodynia	1	0		
Hepatic function abnormal	1	0		
Hepatitis acute	1	0		
Hypercreatininaemia	1	0		
Hypertransaminasaemia	1	0		
Hypothyroidism	1	0		
Influenza like illness	1	0		
Mental status changes	1	0		
Mucosal inflammation	1	0		
Myalgia	1	0		
Myocardial infarction	1	0		
Myocarditis	1	0		
Necrosis	1	0		
Nephrotic syndrome	1	0		
Neutropenia	1	0		
Oedema peripheral	1	0		
Pancytopenia	1	0		
Post procedural infection	1	0		
Presyncope	1	0		
Pyrexia	1	0		
Stomatitis	1	0		

Therapeutic response unexpected	1	0		
Tremor	1	0		
Vena cava thrombosis	1	0		
Vertigo	1	0		
Agitated depression	0	1		
Angina unstable	0	1		
Brain cancer metastatic	0	1		
Hepatitis	0	1		
Hypersensitivity	0	1		
Metastases to lung	0	1		
Mood altered	0	1		
Renal impairment	0	1		
Tinnitus	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Cycle 1 (Day 1 & Day 28); subsequent cycles (Day 1); end of treatment/withdrawal and 28 days post-treatment, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later

Adverse event reporting additional description:

Subjects were followed for AEs from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study medication-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Sunitinib
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Reporting group description:

Subjects received Sunitinib on 9 6-week cycles on 4/2 dosing schedule: 4 weeks on, 2 weeks off.

Reporting group title	Placebo
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Reporting group description:

Subjects received Placebo on 9 6-week cycles with 4/2 dosing schedule: 4 weeks on, 2 weeks off.

Serious adverse events	Sunitinib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 306 (21.90%)	52 / 304 (17.11%)	
number of deaths (all causes)	67	76	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of bladder			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the gastrointestinal tract			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Papillary thyroid cancer			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axonal neuropathy			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	8 / 306 (2.61%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	7 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastrectomy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenectomy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	5 / 306 (1.63%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	5 / 306 (1.63%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	4 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitated depression			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ejection fraction decreased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (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			
Arthropod bite			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incisional hernia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
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	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			

subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	7 / 306 (2.29%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	7 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (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	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (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			
Rash			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Albuminuria			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
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 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritonitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (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	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 306 (0.33%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sunitinib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	303 / 306 (99.02%)	270 / 304 (88.82%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of bladder			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	

Benign neoplasm of thyroid gland subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Brain cancer metastatic subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Cancer pain subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Dysplastic naevus subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Haemangioma subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Lipoma subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	
Malignant melanoma subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Seborrhoeic keratosis subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Tumour haemorrhage subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Tumour pain subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	2 / 304 (0.66%) 2	
Vascular disorders Aortic aneurysm subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Arteriosclerosis			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Capillary disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Embolism venous		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Endothelial dysfunction		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Flushing		
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	4	1
Haematoma		
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	3	1
Hot flush		
subjects affected / exposed	4 / 306 (1.31%)	3 / 304 (0.99%)
occurrences (all)	7	3
Hypertension		
subjects affected / exposed	112 / 306 (36.60%)	35 / 304 (11.51%)
occurrences (all)	179	44
Hypertensive crisis		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Hypotension		
subjects affected / exposed	4 / 306 (1.31%)	3 / 304 (0.99%)
occurrences (all)	4	3
Infarction		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pallor		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Peripheral coldness		

subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	1 / 304 (0.33%) 1	
Phlebitis subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	
Phlebolith subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Poor peripheral circulation subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Surgical and medical procedures			
Abdominal hernia repair subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Cancer surgery subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Dental implantation subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Hysterectomy subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Injection subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Palatal operation subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Spleen operation subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Therapeutic procedure subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	

Tooth extraction subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	1 / 304 (0.33%) 2	
Wisdom teeth removal subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 2	0 / 304 (0.00%) 0	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	69 / 306 (22.55%) 198	36 / 304 (11.84%) 70	
Chest discomfort subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 4	2 / 304 (0.66%) 4	
Chest pain subjects affected / exposed occurrences (all)	11 / 306 (3.59%) 15	13 / 304 (4.28%) 14	
Chills subjects affected / exposed occurrences (all)	10 / 306 (3.27%) 12	4 / 304 (1.32%) 4	
Cyst subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Death subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Face oedema subjects affected / exposed occurrences (all)	28 / 306 (9.15%) 38	1 / 304 (0.33%) 1	
Facial pain subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	112 / 306 (36.60%) 259	74 / 304 (24.34%) 114	
Feeling abnormal			

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Feeling cold		
subjects affected / exposed	4 / 306 (1.31%)	2 / 304 (0.66%)
occurrences (all)	6	2
Feeling hot		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	4
Feeling of body temperature change		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
General physical health deterioration		
subjects affected / exposed	3 / 306 (0.98%)	2 / 304 (0.66%)
occurrences (all)	3	2
Generalised oedema		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Hernia		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Hypothermia		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Impaired healing		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Influenza like illness		
subjects affected / exposed	11 / 306 (3.59%)	5 / 304 (1.64%)
occurrences (all)	16	6
Infusion site extravasation		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Injection site haematoma		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Injection site inflammation		

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Localised oedema		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Malaise		
subjects affected / exposed	6 / 306 (1.96%)	1 / 304 (0.33%)
occurrences (all)	12	2
Mucosal dryness		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	6	1
Mucosal induration		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Mucosal inflammation		
subjects affected / exposed	102 / 306 (33.33%)	25 / 304 (8.22%)
occurrences (all)	246	26
Necrosis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Oedema		
subjects affected / exposed	10 / 306 (3.27%)	2 / 304 (0.66%)
occurrences (all)	17	3
Oedema mucosal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Oedema peripheral		
subjects affected / exposed	24 / 306 (7.84%)	16 / 304 (5.26%)
occurrences (all)	36	17
Pain		
subjects affected / exposed	9 / 306 (2.94%)	9 / 304 (2.96%)
occurrences (all)	11	10
Peripheral swelling		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	4	0
Pyrexia		

subjects affected / exposed	32 / 306 (10.46%)	17 / 304 (5.59%)	
occurrences (all)	45	21	
Secretion discharge			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Swelling			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Temperature intolerance			
subjects affected / exposed	4 / 306 (1.31%)	0 / 304 (0.00%)	
occurrences (all)	4	0	
Therapeutic response unexpected			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Xerosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Mucosal discolouration			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Sensation of foreign body			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Drug hypersensitivity			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	3 / 306 (0.98%)	5 / 304 (1.64%)	
occurrences (all)	3	6	
Seasonal allergy			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	

Social circumstances			
Disability			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Walking disability			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Balanoposthitis			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	5	0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 306 (0.00%)	3 / 304 (0.99%)	
occurrences (all)	0	3	
Breast engorgement			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Breast tenderness			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Erectile dysfunction			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Genital rash			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Gynaecomastia			
subjects affected / exposed	0 / 306 (0.00%)	3 / 304 (0.99%)	
occurrences (all)	0	3	
Haemospermia			

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Menometrorrhagia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Menorrhagia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Ovarian cyst		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Ovarian disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pelvic pain		
subjects affected / exposed	2 / 306 (0.65%)	2 / 304 (0.66%)
occurrences (all)	2	2
Penile pain		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Prostatitis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Prostatomegaly		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Scrotal erythema		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Scrotal pain		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Testicular pain		
subjects affected / exposed	0 / 306 (0.00%)	3 / 304 (0.99%)
occurrences (all)	0	3
Testicular swelling		

subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Testis discomfort subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Vulvovaginal dryness subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Asphyxia subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Bronchial hyperreactivity subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Bronchial obstruction subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	22 / 306 (7.19%) 24	20 / 304 (6.58%) 24	
Dry throat subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	2 / 304 (0.66%) 2	
Dysphonia subjects affected / exposed occurrences (all)	10 / 306 (3.27%) 12	5 / 304 (1.64%) 5	
Dyspnoea subjects affected / exposed occurrences (all)	17 / 306 (5.56%) 20	19 / 304 (6.25%) 23	
Dyspnoea exertional subjects affected / exposed occurrences (all)	5 / 306 (1.63%) 6	4 / 304 (1.32%) 5	
Epistaxis			

subjects affected / exposed	55 / 306 (17.97%)	9 / 304 (2.96%)
occurrences (all)	92	9
Haemoptysis		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Hiccups		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	3	0
Hydrothorax		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Laryngeal pain		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Lung disorder		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Lung infiltration		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Nasal congestion		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	4	0
Nasal discomfort		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Nasal disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	3	0
Nasal dryness		
subjects affected / exposed	5 / 306 (1.63%)	1 / 304 (0.33%)
occurrences (all)	5	1
Nasal inflammation		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Oropharyngeal discomfort		

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Oropharyngeal pain		
subjects affected / exposed	17 / 306 (5.56%)	10 / 304 (3.29%)
occurrences (all)	29	11
Pharyngeal erythema		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pharyngeal ulceration		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pleural effusion		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pneumonitis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Productive cough		
subjects affected / exposed	0 / 306 (0.00%)	5 / 304 (1.64%)
occurrences (all)	0	5
Pulmonary embolism		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	2
Respiratory disorder		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Respiratory tract haemorrhage		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Rhinalgia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Rhinitis allergic		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Rhinorrhoea		

subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 6	5 / 304 (1.64%) 5	
Sneezing subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Sputum discoloured subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	2 / 304 (0.66%) 2	
Tachypnoea subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Throat irritation subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 2	
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Wheezing subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	2 / 304 (0.66%) 2	
Psychiatric disorders			
Affective disorder subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	2 / 304 (0.66%) 2	
Agitated depression subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 2	
Agitation subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Anger subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	

Anxiety		
subjects affected / exposed	10 / 306 (3.27%)	14 / 304 (4.61%)
occurrences (all)	10	15
Apathy		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Confusional state		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Depressed mood		
subjects affected / exposed	3 / 306 (0.98%)	4 / 304 (1.32%)
occurrences (all)	3	4
Depression		
subjects affected / exposed	3 / 306 (0.98%)	10 / 304 (3.29%)
occurrences (all)	5	10
Insomnia		
subjects affected / exposed	30 / 306 (9.80%)	19 / 304 (6.25%)
occurrences (all)	39	21
Irritability		
subjects affected / exposed	5 / 306 (1.63%)	4 / 304 (1.32%)
occurrences (all)	6	5
Listless		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Mental disorder		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Mood altered		
subjects affected / exposed	5 / 306 (1.63%)	3 / 304 (0.99%)
occurrences (all)	5	4
Nervousness		
subjects affected / exposed	4 / 306 (1.31%)	2 / 304 (0.66%)
occurrences (all)	4	2
Persecutory delusion		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0

Sleep disorder			
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)	
occurrences (all)	3	1	
Stress			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Tension			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences (all)	1	1	
Cholecystitis acute			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Cholelithiasis			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences (all)	3	1	
Hepatic steatosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Hepatitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Hepatitis acute			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Hepatotoxicity			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	5 / 306 (1.63%)	2 / 304 (0.66%)	
occurrences (all)	10	3	
Hypertransaminasaemia			

subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 3	1 / 304 (0.33%) 1	
Jaundice subjects affected / exposed occurrences (all)	20 / 306 (6.54%) 22	0 / 304 (0.00%) 0	
Liver disorder subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Portal vein thrombosis subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Investigations			
Alanine aminotransferase subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 2	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	15 / 306 (4.90%) 21	3 / 304 (0.99%) 3	
Amylase increased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 2	0 / 304 (0.00%) 0	
Aspartate aminotransferase subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 2	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	16 / 306 (5.23%) 20	2 / 304 (0.66%) 6	
Basophil count increased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Blood albumin decreased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Blood alkaline phosphatase increased			

subjects affected / exposed occurrences (all)	3 / 306 (0.98%) 4	1 / 304 (0.33%) 3
Blood bicarbonate increased subjects affected / exposed occurrences (all)	3 / 306 (0.98%) 3	2 / 304 (0.66%) 2
Blood bilirubin increased subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 4	1 / 304 (0.33%) 4
Blood calcium decreased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0
Blood chloride decreased subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1
Blood chloride increased subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1
Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0
Blood creatine abnormal subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1
Blood creatine increased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0
Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 2
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	17 / 306 (5.56%) 26	18 / 304 (5.92%) 22
Blood creatinine increased		

subjects affected / exposed	21 / 306 (6.86%)	24 / 304 (7.89%)
occurrences (all)	28	28
Blood glucose increased		
subjects affected / exposed	4 / 306 (1.31%)	2 / 304 (0.66%)
occurrences (all)	5	3
Blood lactate dehydrogenase decreased		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Blood lactate dehydrogenase increased		
subjects affected / exposed	15 / 306 (4.90%)	3 / 304 (0.99%)
occurrences (all)	16	3
Blood magnesium decreased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Blood potassium decreased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Blood potassium increased		
subjects affected / exposed	0 / 306 (0.00%)	3 / 304 (0.99%)
occurrences (all)	0	3
Blood pressure diastolic increased		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Blood pressure increased		
subjects affected / exposed	6 / 306 (1.96%)	2 / 304 (0.66%)
occurrences (all)	10	2
Blood pressure orthostatic		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Blood pressure systolic increased		
subjects affected / exposed	1 / 306 (0.33%)	3 / 304 (0.99%)
occurrences (all)	1	3
Blood sodium decreased		

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Blood thyroid stimulating hormone decreased		
subjects affected / exposed	6 / 306 (1.96%)	1 / 304 (0.33%)
occurrences (all)	6	1
Blood thyroid stimulating hormone increased		
subjects affected / exposed	23 / 306 (7.52%)	7 / 304 (2.30%)
occurrences (all)	28	9
Blood triglycerides increased		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	3
Blood urea increased		
subjects affected / exposed	5 / 306 (1.63%)	7 / 304 (2.30%)
occurrences (all)	6	9
Blood uric acid increased		
subjects affected / exposed	3 / 306 (0.98%)	2 / 304 (0.66%)
occurrences (all)	5	2
Body temperature increased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Cardiac murmur		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Cardiac stress test abnormal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Chest X-ray abnormal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Ejection fraction decreased		
subjects affected / exposed	3 / 306 (0.98%)	6 / 304 (1.97%)
occurrences (all)	3	6
Electrocardiogram QT interval abnormal		

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Electrocardiogram QT prolonged		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	6	7
Electrocardiogram ST segment abnormal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Electrocardiogram ST segment depression		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Electrocardiogram ST segment elevation		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Electrocardiogram ST-T change		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Electrocardiogram T wave inversion		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Electrocardiogram T wave peaked		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Eosinophil count increased		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Gamma-glutamyltransferase increased		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	5	1
Haemoglobin decreased		
subjects affected / exposed	9 / 306 (2.94%)	2 / 304 (0.66%)
occurrences (all)	10	4
Hepatic enzyme increased		

subjects affected / exposed	2 / 306 (0.65%)	2 / 304 (0.66%)
occurrences (all)	2	3
International normalised ratio increased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Liver function test increased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Low density lipoprotein increased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Monocyte count increased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Neutrophil count		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	7	0
Neutrophil count decreased		
subjects affected / exposed	13 / 306 (4.25%)	3 / 304 (0.99%)
occurrences (all)	27	3
Platelet count		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Platelet count decreased		
subjects affected / exposed	8 / 306 (2.61%)	1 / 304 (0.33%)
occurrences (all)	11	2
Platelet count increased		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Prostatic specific antigen increased		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Protein total decreased		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	3	0

Protein total increased		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Protein urine present		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
QRS axis abnormal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Red blood cell count increased		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Staphylococcus test positive		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Thyroid function test abnormal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Thyroxine decreased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Thyroxine free decreased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Transaminases increased		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Troponin T increased		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Visual acuity tests		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Weight decreased		
subjects affected / exposed	14 / 306 (4.58%)	2 / 304 (0.66%)
occurrences (all)	16	2

Weight increased subjects affected / exposed occurrences (all)	8 / 306 (2.61%) 10	18 / 304 (5.92%) 24	
White blood cell count subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
White blood cell count decreased subjects affected / exposed occurrences (all)	15 / 306 (4.90%) 20	2 / 304 (0.66%) 3	
Xanthochromia subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Red blood cell count decreased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 3	0 / 304 (0.00%) 0	
Urobilinogen urine increased subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Injury, poisoning and procedural complications			
Burn oesophageal subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	
Burn oral cavity subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Chest injury subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	2 / 304 (0.66%) 2	
Contusion subjects affected / exposed occurrences (all)	7 / 306 (2.29%) 9	2 / 304 (0.66%) 2	
Fall subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	2 / 304 (0.66%) 2	
Incisional hernia			

subjects affected / exposed	0 / 306 (0.00%)	7 / 304 (2.30%)
occurrences (all)	0	8
Laceration		
subjects affected / exposed	1 / 306 (0.33%)	3 / 304 (0.99%)
occurrences (all)	1	3
Ligament injury		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Limb injury		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Patella fracture		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Post procedural complication		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Procedural pain		
subjects affected / exposed	2 / 306 (0.65%)	5 / 304 (1.64%)
occurrences (all)	2	5
Rib fracture		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Skin abrasion		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Skin injury		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Soft tissue injury		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Stress fracture		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Wound complication		

subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	2 / 304 (0.66%) 2	
Wound dehiscence subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Congenital, familial and genetic disorders Dermoid cyst subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	5 / 306 (1.63%) 6	1 / 304 (0.33%) 1	
Aortic valve stenosis subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Arrhythmia subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	5 / 304 (1.64%) 5	
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	5 / 304 (1.64%) 5	
Bradycardia subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 2	1 / 304 (0.33%) 1	
Bundle branch block left subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Cardiac failure subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	2 / 304 (0.66%) 2	
Cardiovascular disorder			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Conduction disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Diastolic dysfunction		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Extrasystoles		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Left ventricular dysfunction		
subjects affected / exposed	7 / 306 (2.29%)	3 / 304 (0.99%)
occurrences (all)	10	3
Left ventricular hypertrophy		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Mitral valve incompetence		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Mitral valve prolapse		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Myocardial ischaemia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Myocarditis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Palpitations		
subjects affected / exposed	1 / 306 (0.33%)	3 / 304 (0.99%)
occurrences (all)	1	3
Pericardial effusion		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Pericarditis		

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	2 / 306 (0.65%)	2 / 304 (0.66%)	
occurrences (all)	2	3	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)	
occurrences (all)	1	2	
Tachycardia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences (all)	1	1	
Ventricular hypokinesia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	21 / 306 (6.86%)	0 / 304 (0.00%)	
occurrences (all)	32	0	
Aphonia			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences (all)	1	1	
Balance disorder			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Burning sensation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Carotid arteriosclerosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	

Carotid artery stenosis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Carpal tunnel syndrome		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Cerebral infarction		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Cerebrovascular accident		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Cognitive disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Dementia		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Depressed level of consciousness		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Disturbance in attention		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Dizziness		
subjects affected / exposed	23 / 306 (7.52%)	18 / 304 (5.92%)
occurrences (all)	29	22
Dizziness postural		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Dysaesthesia		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	5	1
Dysgeusia		
subjects affected / exposed	103 / 306 (33.66%)	18 / 304 (5.92%)
occurrences (all)	163	20

Facial nerve disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Facial paralysis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Formication		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	3
Head discomfort		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Headache		
subjects affected / exposed	56 / 306 (18.30%)	36 / 304 (11.84%)
occurrences (all)	84	39
Hyperaesthesia		
subjects affected / exposed	5 / 306 (1.63%)	3 / 304 (0.99%)
occurrences (all)	6	3
Hypoaesthesia		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	4	2
Hypogeusia		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Hypotonia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	9 / 306 (2.94%)	9 / 304 (2.96%)
occurrences (all)	18	12
Loss of consciousness		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Memory impairment		
subjects affected / exposed	4 / 306 (1.31%)	3 / 304 (0.99%)
occurrences (all)	5	4

Migraine		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Muscle contractions involuntary		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Neuralgia		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Neuropathy peripheral		
subjects affected / exposed	7 / 306 (2.29%)	4 / 304 (1.32%)
occurrences (all)	9	5
Paraesthesia		
subjects affected / exposed	12 / 306 (3.92%)	11 / 304 (3.62%)
occurrences (all)	15	15
Parkinson's disease		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Peripheral motor neuropathy		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Peripheral sensory neuropathy		
subjects affected / exposed	2 / 306 (0.65%)	7 / 304 (2.30%)
occurrences (all)	2	12
Polyneuropathy		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Presyncope		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Restless legs syndrome		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Sciatica		
subjects affected / exposed	6 / 306 (1.96%)	0 / 304 (0.00%)
occurrences (all)	6	0

Seizure			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Sensory disturbance			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Sensory loss			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	4	0	
Tongue paralysis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	3 / 306 (0.98%)	3 / 304 (0.99%)	
occurrences (all)	3	3	
Irregular sleep wake rhythm disorder			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	33 / 306 (10.78%)	7 / 304 (2.30%)	
occurrences (all)	65	8	
Eosinopenia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Erythroopenia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Hyperglobulinaemia			

subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Increased tendency to bruise subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Leukocytosis subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Leukopenia subjects affected / exposed occurrences (all)	45 / 306 (14.71%) 93	2 / 304 (0.66%) 3	
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	0 / 304 (0.00%) 0	
Lymphopenia subjects affected / exposed occurrences (all)	8 / 306 (2.61%) 14	1 / 304 (0.33%) 1	
Monocytopenia subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	70 / 306 (22.88%) 193	2 / 304 (0.66%) 3	
Thrombocytopenia subjects affected / exposed occurrences (all)	61 / 306 (19.93%) 87	4 / 304 (1.32%) 8	
Ear and labyrinth disorders			
Deafness subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	
Deafness unilateral subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 2	
Ear discomfort subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	

Ear pain			
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)	
occurrences (all)	3	1	
External ear pain			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Hypoacusis			
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)	
occurrences (all)	4	0	
Meniere's disease			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	5 / 306 (1.63%)	5 / 304 (1.64%)	
occurrences (all)	8	6	
Tympanic membrane perforation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	8 / 306 (2.61%)	12 / 304 (3.95%)	
occurrences (all)	16	13	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)	
occurrences (all)	3	1	
Cataract subcapsular			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage			
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Diplopia			

subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Dry eye		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	6	1
Eye discharge		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Eye haemorrhage		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Eye inflammation		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Eye irritation		
subjects affected / exposed	5 / 306 (1.63%)	0 / 304 (0.00%)
occurrences (all)	6	0
Eye oedema		
subjects affected / exposed	7 / 306 (2.29%)	0 / 304 (0.00%)
occurrences (all)	10	0
Eye pain		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	3	0
Eye pruritus		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Eye swelling		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	6	0
Eyelash discolouration		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Eyelid bleeding		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Eyelid oedema		

subjects affected / exposed	21 / 306 (6.86%)	1 / 304 (0.33%)
occurrences (all)	33	1
Eyelid pain		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Glaucoma		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Lacrimal disorder		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Lacrimal gland enlargement		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Lacrimation increased		
subjects affected / exposed	12 / 306 (3.92%)	1 / 304 (0.33%)
occurrences (all)	16	1
Ocular hyperaemia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Ocular surface disease		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Oscillopsia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Periorbital oedema		
subjects affected / exposed	7 / 306 (2.29%)	0 / 304 (0.00%)
occurrences (all)	15	0
Photophobia		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Photopsia		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Retinopathy hypertensive		

subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	3 / 304 (0.99%) 3	
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	
Visual impairment subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 4	1 / 304 (0.33%) 1	
Gastrointestinal disorders			
Abdominal adhesions subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Abdominal discomfort subjects affected / exposed occurrences (all)	8 / 306 (2.61%) 11	8 / 304 (2.63%) 8	
Abdominal distension subjects affected / exposed occurrences (all)	11 / 306 (3.59%) 14	4 / 304 (1.32%) 4	
Abdominal hernia subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	2 / 304 (0.66%) 2	
Abdominal pain subjects affected / exposed occurrences (all)	42 / 306 (13.73%) 70	15 / 304 (4.93%) 17	
Abdominal pain lower subjects affected / exposed occurrences (all)	7 / 306 (2.29%) 7	1 / 304 (0.33%) 1	
Abdominal pain upper subjects affected / exposed occurrences (all)	40 / 306 (13.07%) 76	13 / 304 (4.28%) 15	
Abdominal rigidity subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	

Abdominal tenderness		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Abnormal faeces		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Anal fissure		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Anal haemorrhage		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	3	0
Anal inflammation		
subjects affected / exposed	6 / 306 (1.96%)	0 / 304 (0.00%)
occurrences (all)	7	0
Anal pruritus		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	5	0
Anal skin tags		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Anorectal discomfort		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	6	1
Anorectal disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Aphthous ulcer		
subjects affected / exposed	12 / 306 (3.92%)	2 / 304 (0.66%)
occurrences (all)	20	2
Bowel movement irregularity		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Breath odour		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	3

Change of bowel habit		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Chapped lips		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Colitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Colitis ulcerative		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	2
Constipation		
subjects affected / exposed	36 / 306 (11.76%)	32 / 304 (10.53%)
occurrences (all)	61	42
Dental caries		
subjects affected / exposed	4 / 306 (1.31%)	0 / 304 (0.00%)
occurrences (all)	4	0
Diarrhoea		
subjects affected / exposed	175 / 306 (57.19%)	65 / 304 (21.38%)
occurrences (all)	459	85
Diverticulum intestinal		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Dry mouth		
subjects affected / exposed	14 / 306 (4.58%)	8 / 304 (2.63%)
occurrences (all)	18	9
Duodenal ulcer		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Duodenitis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Duodenogastric reflux		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	6	0

Dyspepsia		
subjects affected / exposed	82 / 306 (26.80%)	19 / 304 (6.25%)
occurrences (all)	149	23
Dysphagia		
subjects affected / exposed	15 / 306 (4.90%)	1 / 304 (0.33%)
occurrences (all)	24	1
Eructation		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	4	1
Flatulence		
subjects affected / exposed	26 / 306 (8.50%)	14 / 304 (4.61%)
occurrences (all)	32	16
Frequent bowel movements		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Functional gastrointestinal disorder		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	2	1
Gastric mucosa erythema		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Gastritis		
subjects affected / exposed	5 / 306 (1.63%)	4 / 304 (1.32%)
occurrences (all)	5	5
Gastrointestinal disorder		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Gastrointestinal dysplasia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Gastrointestinal hypermotility		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	4	0
Gastrointestinal motility disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0

Gastrointestinal obstruction subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1
Gastrointestinal pain subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	27 / 306 (8.82%) 40	9 / 304 (2.96%) 9
Gingival bleeding subjects affected / exposed occurrences (all)	9 / 306 (2.94%) 14	0 / 304 (0.00%) 0
Gingival oedema subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0
Gingival pain subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 3	1 / 304 (0.33%) 1
Gingival recession subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0
Gingival swelling subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	0 / 304 (0.00%) 0
Gingival ulceration subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0
Glossitis subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 5	1 / 304 (0.33%) 1
Glossodynia subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 6	0 / 304 (0.00%) 0
Haemorrhoidal haemorrhage subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	0 / 304 (0.00%) 0

Haemorrhoids		
subjects affected / exposed	12 / 306 (3.92%)	3 / 304 (0.99%)
occurrences (all)	18	5
Hiatus hernia		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Hyperchlorhydria		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	6	0
Hypoaesthesia oral		
subjects affected / exposed	4 / 306 (1.31%)	0 / 304 (0.00%)
occurrences (all)	5	0
Impaired gastric emptying		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Inguinal hernia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Large intestine polyp		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Lip disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Lip dry		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Lip ulceration		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Loose tooth		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Mouth cyst		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1

Mouth ulceration		
subjects affected / exposed	9 / 306 (2.94%)	3 / 304 (0.99%)
occurrences (all)	16	3
Nausea		
subjects affected / exposed	103 / 306 (33.66%)	42 / 304 (13.82%)
occurrences (all)	213	62
Odynophagia		
subjects affected / exposed	5 / 306 (1.63%)	0 / 304 (0.00%)
occurrences (all)	9	0
Oesophageal pain		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	4	0
Oesophagitis		
subjects affected / exposed	14 / 306 (4.58%)	1 / 304 (0.33%)
occurrences (all)	25	3
Oral discomfort		
subjects affected / exposed	4 / 306 (1.31%)	0 / 304 (0.00%)
occurrences (all)	6	0
Oral disorder		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	4	0
Oral mucosal blistering		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Oral mucosal erythema		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Oral pain		
subjects affected / exposed	7 / 306 (2.29%)	2 / 304 (0.66%)
occurrences (all)	7	2
Oral toxicity		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Palatal oedema		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0

Palatal swelling		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Pancreatic steatosis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Perianal erythema		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Proctalgia		
subjects affected / exposed	7 / 306 (2.29%)	1 / 304 (0.33%)
occurrences (all)	12	1
Proctitis		
subjects affected / exposed	9 / 306 (2.94%)	1 / 304 (0.33%)
occurrences (all)	14	1
Rectal haemorrhage		
subjects affected / exposed	6 / 306 (1.96%)	1 / 304 (0.33%)
occurrences (all)	8	1
Regurgitation		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Salivary hypersecretion		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Sensitivity of teeth		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Stomatitis		
subjects affected / exposed	81 / 306 (26.47%)	13 / 304 (4.28%)
occurrences (all)	154	17
Swollen tongue		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Tongue disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0

Tongue oedema			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Tongue ulceration			
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)	
occurrences (all)	3	1	
Tooth loss			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	5 / 306 (1.63%)	3 / 304 (0.99%)	
occurrences (all)	5	3	
Vomiting			
subjects affected / exposed	55 / 306 (17.97%)	20 / 304 (6.58%)	
occurrences (all)	98	24	
Gingival discomfort			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Tongue discomfort			
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 306 (1.96%)	1 / 304 (0.33%)	
occurrences (all)	14	2	
Alopecia			
subjects affected / exposed	26 / 306 (8.50%)	2 / 304 (0.66%)	
occurrences (all)	27	2	
Blister			
subjects affected / exposed	6 / 306 (1.96%)	1 / 304 (0.33%)	
occurrences (all)	9	1	
Cold sweat			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Dermal cyst			

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Dermatitis		
subjects affected / exposed	5 / 306 (1.63%)	3 / 304 (0.99%)
occurrences (all)	6	3
Dry skin		
subjects affected / exposed	43 / 306 (14.05%)	17 / 304 (5.59%)
occurrences (all)	59	19
Dyshidrotic eczema		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Eczema		
subjects affected / exposed	5 / 306 (1.63%)	3 / 304 (0.99%)
occurrences (all)	8	4
Erythema		
subjects affected / exposed	13 / 306 (4.25%)	10 / 304 (3.29%)
occurrences (all)	19	13
Erythrosis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Exfoliative rash		
subjects affected / exposed	5 / 306 (1.63%)	0 / 304 (0.00%)
occurrences (all)	7	0
Granuloma annulare		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Hair colour changes		
subjects affected / exposed	68 / 306 (22.22%)	7 / 304 (2.30%)
occurrences (all)	78	8
Hair growth abnormal		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Hair texture abnormal		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Hyperhidrosis		

subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	2	2
Hyperkeratosis		
subjects affected / exposed	10 / 306 (3.27%)	2 / 304 (0.66%)
occurrences (all)	13	2
Ingrowing nail		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Keloid scar		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Macule		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Nail bed bleeding		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Nail discolouration		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Nail disorder		
subjects affected / exposed	6 / 306 (1.96%)	2 / 304 (0.66%)
occurrences (all)	7	2
Nail growth abnormal		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Nail toxicity		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	4	0
Night sweats		
subjects affected / exposed	2 / 306 (0.65%)	2 / 304 (0.66%)
occurrences (all)	5	2
Palmar erythema		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	3	0
Palmar-plantar erythrodysesthesia		

syndrome		
subjects affected / exposed	154 / 306 (50.33%)	31 / 304 (10.20%)
occurrences (all)	505	42
Panniculitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Papule		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Petechiae		
subjects affected / exposed	5 / 306 (1.63%)	0 / 304 (0.00%)
occurrences (all)	5	0
Photosensitivity reaction		
subjects affected / exposed	3 / 306 (0.98%)	2 / 304 (0.66%)
occurrences (all)	3	2
Pigmentation disorder		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Plantar erythema		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pruritus		
subjects affected / exposed	21 / 306 (6.86%)	21 / 304 (6.91%)
occurrences (all)	31	30
Pruritus generalised		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	4	0
Psoriasis		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Rash		
subjects affected / exposed	59 / 306 (19.28%)	29 / 304 (9.54%)
occurrences (all)	79	42
Rash erythematous		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2

Rash follicular		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Rash generalised		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Rash macular		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	9	1
Rash papular		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Rash vesicular		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Scar pain		
subjects affected / exposed	1 / 306 (0.33%)	7 / 304 (2.30%)
occurrences (all)	1	8
Seborrhoeic dermatitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Skin burning sensation		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	2	1
Skin depigmentation		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Skin discolouration		
subjects affected / exposed	24 / 306 (7.84%)	1 / 304 (0.33%)
occurrences (all)	27	1
Skin disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Skin exfoliation		
subjects affected / exposed	11 / 306 (3.59%)	0 / 304 (0.00%)
occurrences (all)	18	0

Skin fissures		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	5	0
Skin hyperpigmentation		
subjects affected / exposed	12 / 306 (3.92%)	2 / 304 (0.66%)
occurrences (all)	13	2
Skin hypertrophy		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Skin hypopigmentation		
subjects affected / exposed	9 / 306 (2.94%)	1 / 304 (0.33%)
occurrences (all)	10	1
Skin irritation		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Skin lesion		
subjects affected / exposed	9 / 306 (2.94%)	2 / 304 (0.66%)
occurrences (all)	14	2
Skin mass		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Skin odour abnormal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Skin reaction		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Skin toxicity		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Splinter haemorrhages		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Swelling face		
subjects affected / exposed	5 / 306 (1.63%)	0 / 304 (0.00%)
occurrences (all)	13	0

Urticaria			
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)	
occurrences (all)	4	1	
Urticaria thermal			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Yellow skin			
subjects affected / exposed	33 / 306 (10.78%)	2 / 304 (0.66%)	
occurrences (all)	46	3	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	2	0	
Albuminuria			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	2	
Bladder disorder			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Bladder pain			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Bladder spasm			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Chromaturia			
subjects affected / exposed	9 / 306 (2.94%)	0 / 304 (0.00%)	
occurrences (all)	19	0	
Dysuria			
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)	
occurrences (all)	1	1	
Haematuria			
subjects affected / exposed	7 / 306 (2.29%)	5 / 304 (1.64%)	
occurrences (all)	11	6	
Nocturia			

subjects affected / exposed	1 / 306 (0.33%)	6 / 304 (1.97%)
occurrences (all)	2	6
Pollakiuria		
subjects affected / exposed	0 / 306 (0.00%)	3 / 304 (0.99%)
occurrences (all)	0	3
Proteinuria		
subjects affected / exposed	18 / 306 (5.88%)	9 / 304 (2.96%)
occurrences (all)	27	10
Pyelocaliectasis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Renal cyst		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Renal failure		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Renal impairment		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Renal pain		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Urinary incontinence		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Urinary retention		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Urinary tract obstruction		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Endocrine disorders		
Goitre		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2

Hyperparathyroidism			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Hyperthyroidism			
subjects affected / exposed	12 / 306 (3.92%)	2 / 304 (0.66%)	
occurrences (all)	13	2	
Hypothyroidism			
subjects affected / exposed	56 / 306 (18.30%)	4 / 304 (1.32%)	
occurrences (all)	73	4	
Oestrogen deficiency			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Thyroid disorder			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Thyroid mass			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 306 (11.44%)	29 / 304 (9.54%)	
occurrences (all)	52	34	
Arthritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	28 / 306 (9.15%)	26 / 304 (8.55%)	
occurrences (all)	33	29	
Bone pain			
subjects affected / exposed	4 / 306 (1.31%)	8 / 304 (2.63%)	
occurrences (all)	5	8	
Bursitis			
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)	
occurrences (all)	0	2	
Fibromyalgia			

subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Flank pain		
subjects affected / exposed	3 / 306 (0.98%)	4 / 304 (1.32%)
occurrences (all)	3	6
Groin pain		
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	4	1
Haemarthrosis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Interspinous osteoarthritis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Intervertebral disc disorder		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Joint stiffness		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Joint swelling		
subjects affected / exposed	4 / 306 (1.31%)	2 / 304 (0.66%)
occurrences (all)	4	2
Limb discomfort		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Muscle fatigue		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Muscle mass		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Muscle spasms		
subjects affected / exposed	25 / 306 (8.17%)	13 / 304 (4.28%)
occurrences (all)	30	13
Muscular weakness		

subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	3	1
Musculoskeletal chest pain		
subjects affected / exposed	7 / 306 (2.29%)	4 / 304 (1.32%)
occurrences (all)	7	4
Musculoskeletal discomfort		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	2
Musculoskeletal disorder		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Musculoskeletal pain		
subjects affected / exposed	13 / 306 (4.25%)	14 / 304 (4.61%)
occurrences (all)	16	17
Musculoskeletal stiffness		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Myalgia		
subjects affected / exposed	25 / 306 (8.17%)	15 / 304 (4.93%)
occurrences (all)	32	15
Myalgia intercostal		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Myositis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Neck pain		
subjects affected / exposed	5 / 306 (1.63%)	5 / 304 (1.64%)
occurrences (all)	10	5
Nodal osteoarthritis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Osteoarthritis		
subjects affected / exposed	4 / 306 (1.31%)	3 / 304 (0.99%)
occurrences (all)	4	3
Osteochondrosis		

subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Osteoporosis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Osteoporosis postmenopausal		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pain in extremity		
subjects affected / exposed	45 / 306 (14.71%)	20 / 304 (6.58%)
occurrences (all)	63	23
Periarthritis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Rhabdomyolysis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Soft tissue disorder		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Spinal column stenosis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Spinal osteoarthritis		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Spinal pain		
subjects affected / exposed	8 / 306 (2.61%)	2 / 304 (0.66%)
occurrences (all)	9	2
Synovial cyst		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Tendonitis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Tenosynovitis		

subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Infections and infestations			
Angular cheilitis subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Bronchitis subjects affected / exposed occurrences (all)	6 / 306 (1.96%) 7	6 / 304 (1.97%) 6	
Bronchitis viral subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 2	0 / 304 (0.00%) 0	
Candida infection subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Cellulitis subjects affected / exposed occurrences (all)	3 / 306 (0.98%) 3	0 / 304 (0.00%) 0	
Conjunctivitis subjects affected / exposed occurrences (all)	8 / 306 (2.61%) 12	4 / 304 (1.32%) 6	
Cystitis subjects affected / exposed occurrences (all)	3 / 306 (0.98%) 3	2 / 304 (0.66%) 3	
Diverticulitis subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Ear infection subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 3	4 / 304 (1.32%) 4	
Enteritis infectious subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Erysipelas subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	

Folliculitis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Fungal infection		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	3	0
Fungal skin infection		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Gastroenteritis		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Gastroenteritis viral		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Genital candidiasis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Genital herpes		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Gingivitis		
subjects affected / exposed	8 / 306 (2.61%)	0 / 304 (0.00%)
occurrences (all)	8	0
Helicobacter gastritis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Herpes simplex		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Herpes virus infection		
subjects affected / exposed	5 / 306 (1.63%)	1 / 304 (0.33%)
occurrences (all)	5	1
Herpes zoster		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0

Hordeolum		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Influenza		
subjects affected / exposed	6 / 306 (1.96%)	3 / 304 (0.99%)
occurrences (all)	7	6
Laryngitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Liver abscess		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	3	0
Lower respiratory tract infection		
subjects affected / exposed	0 / 306 (0.00%)	4 / 304 (1.32%)
occurrences (all)	0	4
Lung infection		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	1
Nasopharyngitis		
subjects affected / exposed	15 / 306 (4.90%)	20 / 304 (6.58%)
occurrences (all)	16	25
Oral herpes		
subjects affected / exposed	7 / 306 (2.29%)	3 / 304 (0.99%)
occurrences (all)	8	4
Oral infection		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Osteomyelitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Otitis externa		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0

Paronychia		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Periodontitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	3	0
Peritonsillitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	2	0
Pharyngitis		
subjects affected / exposed	6 / 306 (1.96%)	5 / 304 (1.64%)
occurrences (all)	6	5
Pharyngitis streptococcal		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Pilonidal cyst		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Post procedural infection		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Postoperative wound infection		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Pulpitis dental		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Respiratory tract infection		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Retinitis		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1

Rhinitis		
subjects affected / exposed	7 / 306 (2.29%)	3 / 304 (0.99%)
occurrences (all)	7	3
Rhinolaryngitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Sinobronchitis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Sinusitis		
subjects affected / exposed	4 / 306 (1.31%)	2 / 304 (0.66%)
occurrences (all)	10	2
Skin infection		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Staphylococcal scalded skin syndrome		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Tinea pedis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Tooth abscess		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	2	0
Tooth infection		
subjects affected / exposed	3 / 306 (0.98%)	2 / 304 (0.66%)
occurrences (all)	4	2
Tracheitis		
subjects affected / exposed	0 / 306 (0.00%)	2 / 304 (0.66%)
occurrences (all)	0	2
Upper respiratory tract infection		
subjects affected / exposed	6 / 306 (1.96%)	5 / 304 (1.64%)
occurrences (all)	6	5
Urinary tract infection		

subjects affected / exposed occurrences (all)	7 / 306 (2.29%) 16	7 / 304 (2.30%) 11	
Urogenital infection fungal subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Vaginal infection subjects affected / exposed occurrences (all)	2 / 306 (0.65%) 2	1 / 304 (0.33%) 1	
Viral hepatitis carrier subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Viral infection subjects affected / exposed occurrences (all)	4 / 306 (1.31%) 4	0 / 304 (0.00%) 0	
Viral labyrinthitis subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Vulvitis subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	1 / 304 (0.33%) 1	
Wound infection subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	1 / 304 (0.33%) 1	
Eye infection subjects affected / exposed occurrences (all)	0 / 306 (0.00%) 0	2 / 304 (0.66%) 2	
Metabolism and nutrition disorders			
Alkalosis subjects affected / exposed occurrences (all)	1 / 306 (0.33%) 1	0 / 304 (0.00%) 0	
Decreased appetite subjects affected / exposed occurrences (all)	59 / 306 (19.28%) 99	16 / 304 (5.26%) 20	

Diabetes mellitus		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	3
Dyslipidaemia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Fluid retention		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Gout		
subjects affected / exposed	4 / 306 (1.31%)	1 / 304 (0.33%)
occurrences (all)	4	1
Hypercalcaemia		
subjects affected / exposed	1 / 306 (0.33%)	1 / 304 (0.33%)
occurrences (all)	1	2
Hypercholesterolaemia		
subjects affected / exposed	3 / 306 (0.98%)	7 / 304 (2.30%)
occurrences (all)	3	10
Hypercreatininaemia		
subjects affected / exposed	2 / 306 (0.65%)	0 / 304 (0.00%)
occurrences (all)	3	0
Hyperglycaemia		
subjects affected / exposed	9 / 306 (2.94%)	11 / 304 (3.62%)
occurrences (all)	10	18
Hyperkalaemia		
subjects affected / exposed	1 / 306 (0.33%)	3 / 304 (0.99%)
occurrences (all)	1	3
Hyperlipidaemia		
subjects affected / exposed	2 / 306 (0.65%)	1 / 304 (0.33%)
occurrences (all)	2	1
Hypertriglyceridaemia		
subjects affected / exposed	3 / 306 (0.98%)	2 / 304 (0.66%)
occurrences (all)	9	2
Hyperuricaemia		
subjects affected / exposed	4 / 306 (1.31%)	5 / 304 (1.64%)
occurrences (all)	7	6

Hypoalbuminaemia		
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	3	1
Hypocalcaemia		
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	3	1
Hypoglycaemia		
subjects affected / exposed	0 / 306 (0.00%)	3 / 304 (0.99%)
occurrences (all)	0	4
Hypokalaemia		
subjects affected / exposed	3 / 306 (0.98%)	0 / 304 (0.00%)
occurrences (all)	5	0
Hypomagnesaemia		
subjects affected / exposed	1 / 306 (0.33%)	2 / 304 (0.66%)
occurrences (all)	1	2
Hyponatraemia		
subjects affected / exposed	3 / 306 (0.98%)	1 / 304 (0.33%)
occurrences (all)	6	1
Hypophagia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Hypophosphataemia		
subjects affected / exposed	7 / 306 (2.29%)	3 / 304 (0.99%)
occurrences (all)	14	4
Hypoproteinaemia		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Hypovitaminosis		
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)
occurrences (all)	1	0
Increased appetite		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1
Iron deficiency		
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)
occurrences (all)	0	1

Malnutrition			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 306 (0.00%)	1 / 304 (0.33%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	1 / 306 (0.33%)	0 / 304 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2007	Changed treatment administration from 37.5 mg continuous dosing to 50 mg Schedule 4/2, and duration of treatment from 2 years to 1 year. • Sample size was re estimated and the number of DFS changed from 127 to 101 events. • Included that the primary DFS analysis will be based on independent blinded third party review and DFS based on investigator assessments as a secondary analysis. • Removed Relapse Free Survival as a secondary endpoint. • Added an additional interim analysis after the first 75 events (75% of the events) had occurred. • Added UISS Prognostic Model. • Added the collection of blood and tumor tissue samples for subsequent de identified.
18 April 2007	Clarified how suspected unexpected serious adverse event reactions would be reported. • Statement that adequate contraception was to be used by fertile patients was added. The definition of adequate contraception was outlined in the protocol.
24 July 2007	Amendment was not released.
01 January 2008	Deleted visits Cycle 1 Day 15 and Cycle 2 Day 15, and added visit Cycle 1 Day 28. • Added laboratory tests: (TSH, creatine phosphokinase, and magnesium). • Added 12 lead ECG at Cycle 1 Day 28 and at 3, 6, and 12 months or for cause. • Added 2 D ECHO or MUGA at 3, 6 and 12 months or for cause. • Prolonged time period between surgery and randomization/start treatment to 12 weeks. • Deleted pre nephrectomy ECOG PS (ECOG PS needs to be determined prior to randomization and dosing). • Revised collection of survival status information to every 12 weeks instead of every 3 months by telephone. • Extended the maximum allowable time of treatment for toxicity issues to 6 weeks rather than 4 weeks.
01 January 2008	(Country specific: United Kingdom) • The changes made in Amendment 4 were included in this amendment. • Inclusion Criterion 12 and Life Style Guidelines section were updated to provide clarification of language regarding acceptable barrier contraception methods.
19 June 2008	Urinalysis was included for assessment of proteinuria. • Group a. was extended to T3 N0 or NX, M0, any Fuhrman's grade, and any ECOG PS. • Added statement that pre nephrectomy ECOG evaluation was the preferred baseline measure. • Instructions were provided regarding the addition of ECGs to be completed for inpatient sunitinib dose modification. • The timing of the additional MUGA or ECHO assessments was clarified to better correlate the request for testing at 3, 6, and 12 months. • Exclusion criterion 17 and the Life Style Guidelines were modified to reiterate that patients had to agree to continue using adequate contraception for 3 months after the last dose of study treatment. • Additional CYP3A4 inhibitors were added to the concomitant medication section. • Instructions on when additional ECGs were to be performed in the safety assessment section of the protocol were added. • Clarified that this clinical study used the Investigator's Brochure as the reference document for determining expectedness of AEs for regulatory purposes. • Several regulatory agencies required reporting of study results at the end of each clinical study. The definition of "End of Trial" was clarified in this study. The End of Trial was defined as the date of the final data point to be included in the final CSR. • Appendix 1 was updated to included magnesium and urinalysis based on above rationale for revised ECG monitoring and proteinuria monitoring. • Sections 11, 12, and 13 of the protocol were updated based on revised protocol template language for all clinical studies at Pfizer. • Minor administrative changes were made to correct typographical errors, emphasize subtle points or improve internal consistency and clarity of the protocol.

28 April 2009	Sample size was re calculated based on population changes in Amendment 6 and updated survival analysis in the mRCC population. • The assumptions of 2 year DFS rates for the placebo treatment group and sunitinib treatment group for the 3 risk groups were revised. • The minimal number DFS events required to detect the statistical difference in DFS between the 2 treatment groups was increased from 101 to 320 DFS events. • The estimated number of patients to enroll increased from 236 to 500 patients. • Coagulation tests (prothrombin time and international normalized ratio) at screening were removed.
17 February 2010	Amendment not implemented due to differences between the amendment and the Molecular Profiling supplement: • Pharmacogenomics blood samples were increased. • End of study/withdrawal procedures section was updated. • 21 new sites and 1 country (China) were added. • Statistical analysis was updated and some clarifications added.
20 June 2010	The changes made in Amendment 8 (not released) were included in this amendment. • Tumor images including CT or MRI of chest, abdomen, and pelvis were to be performed every 12 weeks at Day 1 of Cycles 3, 5, 7, and 9 (odd numbered cycles). • Included blood collection pre dose for patients who signed Part II of the ICD on Cycle 1 Day 1 and Day 28 for DNA, RNA, and biomarker analyses and at end of treatment/withdrawal for RNA and biomarker analyses at time of recurrence. • Criteria for fertility will be provided in SAP. • For the second interim analysis, re estimate the sample size by the method outlined by Cui will be employed, which will preserve the type I error at the target rate. • Number of years that some patients will be followed for survival increased from 7 to 8 years.
20 April 2011	120 Chinese patients to estimate an improvement of DFS in Chinese patients at the high risk of recurrent RCC were added. Analyses of this Chinese subpopulation will be provided in a separate report.
04 October 2011	The timing of the first interim analysis was adjusted. • Number of patients was increased from 500 to 600. • Collection time point of Prep D1 (whole blood collection optimized for DNA analysis) and blood volume of Molecular Profiling samples was corrected.
09 October 2011	Guidance for potential cases of drug induced liver injury was added. • The sponsor's IOBU SDMC information was included. • AE reporting period was clarified. • Publications were updated.
14 June 2012	Summary Rationale and Introduction safety and efficacy sections were updated according to the most updated information. • Medication errors language was updated to align with CT 3 guidance on the collection, verification and presentation of adverse reaction reports arising from clinical studies on medicinal products for human use. • AE reporting section updated due to alignment with CT 3 guidance (effective 11 June 2011) and US FDA Final Rule (effective 28 September 2011).
17 July 2014	Time for final analysis was changed to 5 years after LSFV or when approximately 258 DFS events had occurred. • Data analysis/statistical methods and study design sections were updated to be in line with new time for final analysis. • AE reporting period section was updated. • Medication errors section was moved to Section 8 and minor administrative changes were made to align with the last version of the protocol template. • China specific study design information was added. • Exclusion criterion regarding contraception was revised. • Appendices 10, 11 and 12 were removed and summary of changes for Amendments 7, 8, and 9 were included.

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

Notes: