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	

Results information

Result version number	v1
This version publication date	23 March 2017
First version publication date	23 March 2017

Trial information

Trial identification

Sponsor protocol code	A6181109

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	Interim
Date of interim/final analysis	07 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate an improvement in disease-free survival (DFS) in patients 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:

This study was conducted in compliance with the ethical principles originating in or derived from the declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 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:

The study was conducted at 97 centers in Australia, China, Colombia, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Malaysia, Poland, Korea, Slovakia, Spain, Sweden, Switzerland, Taiwan, United Kingdom, and United States. All the enrolled participants were included in the trial.

Pre-assignment

Screening details:

The study consisted of 2 cohorts, a Global cohort and a China cohort. The data from the China cohort is intended to be analyzed separately. Follow-up is currently ongoing in the China cohort. The focus of this summary is the Global cohort. Data cut off date: Global cohort: 07Apr16 China cohort (projected): Sep17

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:

Participants 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. Patients experiencing toxicity were managed by treatment interruption or dose reduction to 37.5 mg QD, and/or permanent discontinuation from study treatment.

Arm title	Placebo

Arm description:

Participants 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. Patients 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
Completed	186	191
Not completed	123	115
Death	61	64
Other	24	16
Subject refused further follow-up	24	23
Lost to follow-up	14	12

Baseline characteristics

Reporting groups	
Reporting group title	Sunitinib
Reporting group description:	
Participants 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:	
Participants 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			
Adults (18-64 years)	233	224	457
From 65-84 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:	
Participants 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:	
Participants 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 was defined as the time interval (in years) from the date of randomization to the first date of recurrence or occurrence of a secondary malignancy or death. Recurrence refers to relapse of the primary tumor in-situ or at metastatic sites. Date of recurrence or occurrence: The date of the recurrence or occurrence of a secondary malignancy for the first time, either by blinded independent central review (BICR) or investigator assessment for the respective analyses. Participants 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.	
End point type	Primary
End point timeframe:	
Every 12 weeks during the first 3 years and every 6 months after that unless the patient had withdrawn consent	

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 9999)	5.6 (3.8 to 6.6)		

Statistical analyses

Statistical analysis title	DFS- Assessed by BICR
Comparison groups	Sunitinib v Placebo

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 UISS High Risk Group-Intent to Treat Population)

End point title	DFS- Assessed by the Investigator (Stratified by UISS High Risk Group-Intent to Treat Population)

End point description:

DFS was defined as the time interval (in years) from the date of randomization to the first date of recurrence or occurrence of a secondary malignancy or death. Recurrence refers to relapse of the primary tumor in-situ or at metastatic sites. Date of recurrence or occurrence: The date of the recurrence or occurrence of a secondary malignancy for the first time, either by BICR or investigator assessment for the respective analyses. Participants 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.

End point type	Secondary

End point timeframe:

Every 12 weeks during the first 3 years and every 6 months after that unless the patient had withdrawn consent

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)	4.5 (3.8 to 5.9)		

Statistical analyses

Statistical analysis title	DFS- Assessed by the Investigator
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.
OS data were not mature at the time of data cutoff and the median OS was not reached for either arm.

End point type	Secondary

End point timeframe:

Every 12 weeks until 5 years from Last Subject First Visit (LSFV)

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	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	OS- 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	= 0.938
Method	Cox Proportional hazards model
Parameter estimate	Cox proportional hazard
Point estimate	1.014

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.716
upper limit	1.435

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

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

End point description:

TEAEs are all AEs (serious and non-serious) 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 (CTC grade) over the baseline will also be considered TEAEs. Participants 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 participants 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.

End point type	Secondary

End point timeframe:

From Cycle 1/Day 1 until at least 28 days post treatment

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306	304		
Units: Number of participants				
Patients With AEs	305	269		
Patients With Serious Adverse Events (SAEs)	67	52		
Patients With Grade 3 or Grade 4 AEs	189	61		
Patients With Grade 5 AEs	5	5		
Patients Discontinued Due to AEs	86	17		
Patients With Dose Reduced Due to AEs	105	6		
Patients With Temporary Discontinuation Due to AEs	142	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)

End point description:

TEAEs are all AEs (serious and non-serious) 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 (CTC grade) over the baseline will also be considered TEAEs. Participants 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 participants 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.

End point type	Secondary

End point timeframe:

From Cycle 1/Day 1 until at least 28 days post treatment

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306	304		
Units: Mean				
arithmetic mean (standard deviation)				
Benign Neoplasm of Thyroid Gland, (n=0,1)	0 (± 0)	35.1 (± 0)		
Goitre, (n=0,2)	0 (± 0)	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)	0 (± 0)	22.1 (± 0)		
Thyroid Disorder, (n=1,0)	19 (± 0)	0 (± 0)		
Thyroid Mass, (n=0,1)	0 (± 0)	20.4 (± 0)		

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

End point description:

PROs was defined as health-related quality of life using the self administered EORTC Quality of Life Questionnaire -C30 (EORTC QLQ-C30) and health status using the EuroQoL Group EQ-5D questionnaire. The EORTC QLQ-C30 measures 5 functional domains of physical, role, cognitive, emotional and social and symptom scales of fatigue, pain, nausea and vomiting, and general health status. Participants completed the questionnaire at the clinic prior to administration of study medications or other clinical activities. End of treatment was defined as collection of the final data point in the study.

End point type	Secondary

End point timeframe:

From Cycle 1/Day 1 or approximately every 6 weeks up to End of treatment

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

End point description:

PROs was defined as health-related quality of life using the self administered EORTC Quality of Life Questionnaire -C30 (EORTC QLQ-C30) and health status using the EuroQoL Group EQ-5D questionnaire. The EORTC QLQ-C30 measures 5 functional domains of physical, role, cognitive, emotional and social and symptom scales of fatigue, pain, nausea and vomiting, and general health status. Participants completed the questionnaire at the clinic prior to administration of study medications or other clinical activities. End of treatment was defined as collection of the final data point in the study.

End point type	Secondary

End point timeframe:

From Cycle 1/ Day 1 or approximately every 6 weeks up to End of treatment

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

End point description:

PROs was defined as health-related quality of life using the self administered EORTC Quality of Life Questionnaire -C30 (EORTC QLQ-C30) and health status using the EuroQoL Group EQ-5D questionnaire. The EORTC QLQ-C30 measures 5 functional domains of physical, role, cognitive, emotional and social and symptom scales of fatigue, pain, nausea and vomiting, and general health status. Participants completed the questionnaire at the clinic prior to administration of study medications or other clinical activities. End of treatment was defined as collection of the final data point in the study.

End point type	Secondary

End point timeframe:

From Cycle 1/ Day 1 or approximately every 6 weeks up to End of treatment

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

End point title	PROs- EuroQoL EQ-5D Observed Means

End point description:

PROs was defined as health-related quality of life using the self administered EORTC Quality of Life Questionnaire -C30 (EORTC QLQ-C30) and health status using the EuroQoL Group EQ-5D questionnaire. The EQ-5D comprises of 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). A unique EQ-5D health state was defined by combining one level from each of the 5 dimensions and was converted to a single summary index or health utility value. The EQ- 5D questionnaire was completed during each clinic visit prior to any other interventions. End of treatment was defined as collection of the final data point in the study.

End point type	Secondary

End point timeframe:

From Cycle 1/ Day 1 or approximately every 6 weeks up to End of treatment

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

End point description:

PROs was defined as health-related quality of life using the self administered EORTC Quality of Life Questionnaire -C30 (EORTC QLQ-C30) and health status using the EuroQoL Group EQ-5D questionnaire. The EuroQoL EQ-5D consists of 2 parts, the EQ-5D index (or simply EQ-5D) and EQ-VAS. The EQ-VAS is a visual analog scale where the patient indicated how good or bad his health on that day by marking an appropriate point on a line between 0 (worst imaginable health states) to 100 (best imaginable health states). End of treatment was defined as collection of the final data point in the study.

End point type	Secondary

End point timeframe:

From Cycle 1/ Day 1 or approximately every 6 weeks upto End of treatment

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 Participants With Tolerability Symptoms

End point title	Number of Participants With Tolerability Symptoms

End point description:

Participants 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 participants 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.

End point type	Secondary

End point timeframe:

From Cycle 1/Day 1 until 28 days post treatment

End point values	Sunitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	306		
Units: Number of Events]				
number (not applicable)				
Palmar-plantar erythrodysaesthesia 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:

From Day 1 of start of study treatment until Day 28 post treatment.

Adverse event reporting additional description:

Participants 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

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

Reporting group title	Sunitinib

Reporting group description:

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

Serious adverse events	Placebo	Sunitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 304 (17.11%)	67 / 306 (21.90%)	
number of deaths (all causes)	64	63	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute promyelocytic leukaemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

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

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

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

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

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			

subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meniscus injury			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
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	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 304 (0.33%)	7 / 306 (2.29%)	
occurrences causally related to treatment / all	0 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Tympanic membrane perforation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

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

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (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	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

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

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

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

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

Non-serious adverse events	Placebo	Sunitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	269 / 304 (88.49%)	303 / 306 (99.02%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of bladder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Brain cancer metastatic			

subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Cancer pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Lipoma			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Malignant melanoma			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic keratosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Tumour haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tumour pain			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Arteriosclerosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Capillary disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Embolism venous			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Endothelial dysfunction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	

Flushing			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	4	
Surgical and medical procedures			
Abdominal hernia repair			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cancer surgery			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Dental implantation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Hysterectomy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Injection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Palatal operation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Spleen operation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Therapeutic procedure			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Wisdom teeth removal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	36 / 304 (11.84%)	69 / 306 (22.55%)	
occurrences (all)	70	198	
Chest discomfort			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	4	3	
Chest pain			
subjects affected / exposed	13 / 304 (4.28%)	11 / 306 (3.59%)	
occurrences (all)	14	15	
Chills			
subjects affected / exposed	4 / 304 (1.32%)	10 / 306 (3.27%)	
occurrences (all)	4	12	
Cyst			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Death			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	1 / 304 (0.33%)	28 / 306 (9.15%)	
occurrences (all)	1	38	
Facial pain			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	74 / 304 (24.34%)	112 / 306 (36.60%)	
occurrences (all)	114	259	
Feeling abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	2 / 304 (0.66%)	4 / 306 (1.31%)	
occurrences (all)	2	6	
Feeling hot			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	4	0	

Feeling of body temperature change			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	2	3	
Generalised oedema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Hernia			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Hypothermia			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Impaired healing			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	5 / 304 (1.64%)	11 / 306 (3.59%)	
occurrences (all)	6	16	
Infusion site extravasation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Injection site inflammation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Localised oedema			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Malaise			
subjects affected / exposed	1 / 304 (0.33%)	6 / 306 (1.96%)	
occurrences (all)	2	12	

Mucosal dryness			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	6	
Mucosal induration			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Mucosal inflammation			
subjects affected / exposed	25 / 304 (8.22%)	102 / 306 (33.33%)	
occurrences (all)	26	246	
Necrosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	2 / 304 (0.66%)	10 / 306 (3.27%)	
occurrences (all)	3	17	
Oedema mucosal			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	16 / 304 (5.26%)	24 / 306 (7.84%)	
occurrences (all)	17	36	
Pain			
subjects affected / exposed	9 / 304 (2.96%)	9 / 306 (2.94%)	
occurrences (all)	10	11	
Peripheral swelling			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	17 / 304 (5.59%)	32 / 306 (10.46%)	
occurrences (all)	21	45	
Secretion discharge			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	

Temperature intolerance			
subjects affected / exposed	0 / 304 (0.00%)	4 / 306 (1.31%)	
occurrences (all)	0	4	
Therapeutic response unexpected			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Xerosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	5 / 304 (1.64%)	3 / 306 (0.98%)	
occurrences (all)	6	3	
Seasonal allergy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Social circumstances			
Disability			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Walking disability			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Balanoposthitis			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	5	

Breast pain			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Breast tenderness			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Genital rash			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Gynaecomastia			
subjects affected / exposed	3 / 304 (0.99%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Haematospermia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Menometrorrhagia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Menorrhagia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Ovarian disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	2 / 304 (0.66%)	2 / 306 (0.65%)	
occurrences (all)	2	2	
Penile pain			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	

Prostatitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Prostatomegaly			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Scrotal erythema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Scrotal pain			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Testicular pain			
subjects affected / exposed	3 / 304 (0.99%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Testicular swelling			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Testis discomfort			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Vulvovaginal dryness			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Bronchial obstruction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	20 / 304 (6.58%)	22 / 306 (7.19%)	
occurrences (all)	24	24	
Dry throat			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Dysphonia			
subjects affected / exposed	5 / 304 (1.64%)	10 / 306 (3.27%)	
occurrences (all)	5	12	
Dyspnoea			
subjects affected / exposed	19 / 304 (6.25%)	18 / 306 (5.88%)	
occurrences (all)	23	21	
Dyspnoea exertional			
subjects affected / exposed	4 / 304 (1.32%)	5 / 306 (1.63%)	
occurrences (all)	5	6	
Epistaxis			
subjects affected / exposed	9 / 304 (2.96%)	55 / 306 (17.97%)	
occurrences (all)	9	92	
Haemoptysis			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Hiccups			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	3	
Hydrothorax			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Laryngeal pain			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Lung infiltration			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Nasal congestion			

subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	4	
Nasal discomfort			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Nasal disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	3	
Nasal dryness			
subjects affected / exposed	1 / 304 (0.33%)	5 / 306 (1.63%)	
occurrences (all)	1	5	
Nasal inflammation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Oropharyngeal discomfort			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	10 / 304 (3.29%)	17 / 306 (5.56%)	
occurrences (all)	11	29	
Pharyngeal erythema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Pharyngeal ulceration			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Pneumonitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	5 / 304 (1.64%)	0 / 306 (0.00%)	
occurrences (all)	5	0	
Pulmonary embolism			

subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Respiratory disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Rhinalgia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	5 / 304 (1.64%)	4 / 306 (1.31%)	
occurrences (all)	5	6	
Sneezing			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Sputum discoloured			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Tachypnoea			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Wheezing			

subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Agitated depression			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Agitation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Anger			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	14 / 304 (4.61%)	10 / 306 (3.27%)	
occurrences (all)	15	10	
Apathy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	4 / 304 (1.32%)	3 / 306 (0.98%)	
occurrences (all)	4	3	
Depression			
subjects affected / exposed	9 / 304 (2.96%)	3 / 306 (0.98%)	
occurrences (all)	9	5	
Insomnia			
subjects affected / exposed	19 / 304 (6.25%)	30 / 306 (9.80%)	
occurrences (all)	21	39	
Irritability			
subjects affected / exposed	4 / 304 (1.32%)	5 / 306 (1.63%)	
occurrences (all)	5	6	

Listless			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Mental disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Mood altered			
subjects affected / exposed	3 / 304 (0.99%)	5 / 306 (1.63%)	
occurrences (all)	4	5	
Nervousness			
subjects affected / exposed	2 / 304 (0.66%)	4 / 306 (1.31%)	
occurrences (all)	2	5	
Persecutory delusion			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Sleep disorder			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Stress			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tension			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Cholecystitis acute			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	3	
Hepatic steatosis			

subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Hepatitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Hepatitis acute			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hepatotoxicity			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 304 (0.66%)	5 / 306 (1.63%)	
occurrences (all)	3	10	
Hypertransaminasaemia			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	3	
Jaundice			
subjects affected / exposed	0 / 304 (0.00%)	20 / 306 (6.54%)	
occurrences (all)	0	22	
Liver disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Portal vein thrombosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 304 (0.66%)	15 / 306 (4.90%)	
occurrences (all)	2	21	
Amylase increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	

Aspartate aminotransferase				
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)		
occurrences (all)	2	0		
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 304 (0.66%)	16 / 306 (5.23%)		
occurrences (all)	6	20		
Basophil count increased				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Blood albumin decreased				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)		
occurrences (all)	3	4		
Blood bicarbonate increased				
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)		
occurrences (all)	2	3		
Blood bilirubin increased				
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)		
occurrences (all)	4	3		
Blood calcium decreased				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Blood chloride decreased				
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)		
occurrences (all)	1	0		
Blood chloride increased				
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)		
occurrences (all)	1	0		
Blood cholesterol increased				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Blood creatine abnormal				

subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Blood creatine increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	18 / 304 (5.92%)	16 / 306 (5.23%)	
occurrences (all)	22	25	
Blood creatinine increased			
subjects affected / exposed	24 / 304 (7.89%)	21 / 306 (6.86%)	
occurrences (all)	28	28	
Blood glucose increased			
subjects affected / exposed	2 / 304 (0.66%)	4 / 306 (1.31%)	
occurrences (all)	4	5	
Blood lactate dehydrogenase decreased			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 304 (0.99%)	15 / 306 (4.90%)	
occurrences (all)	3	16	
Blood magnesium decreased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Blood potassium increased			
subjects affected / exposed	3 / 304 (0.99%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Blood pressure diastolic increased			

subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Blood pressure increased			
subjects affected / exposed	2 / 304 (0.66%)	6 / 306 (1.96%)	
occurrences (all)	2	10	
Blood pressure orthostatic			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Blood pressure systolic increased			
subjects affected / exposed	3 / 304 (0.99%)	1 / 306 (0.33%)	
occurrences (all)	3	1	
Blood sodium decreased			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 304 (0.33%)	6 / 306 (1.96%)	
occurrences (all)	1	6	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	7 / 304 (2.30%)	23 / 306 (7.52%)	
occurrences (all)	9	28	
Blood triglycerides increased			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Blood urea increased			
subjects affected / exposed	7 / 304 (2.30%)	4 / 306 (1.31%)	
occurrences (all)	9	5	
Blood uric acid increased			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	2	5	
Body temperature increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cardiac murmur			

subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Cardiac stress test abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Chest X-ray abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Ejection fraction decreased			
subjects affected / exposed	6 / 304 (1.97%)	3 / 306 (0.98%)	
occurrences (all)	6	3	
Electrocardiogram QT interval abnormal			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	7	6	
Electrocardiogram ST segment abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram ST-T change			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Electrocardiogram T wave peaked			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Eosinophil count increased			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	5	
Haemoglobin decreased			
subjects affected / exposed	2 / 304 (0.66%)	7 / 306 (2.29%)	
occurrences (all)	4	8	
Hepatic enzyme increased			
subjects affected / exposed	2 / 304 (0.66%)	2 / 306 (0.65%)	
occurrences (all)	3	2	
International normalised ratio increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Low density lipoprotein increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Monocyte count increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Neutrophil count			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	7	
Neutrophil count decreased			
subjects affected / exposed	3 / 304 (0.99%)	12 / 306 (3.92%)	
occurrences (all)	3	27	
Platelet count			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 304 (0.33%)	8 / 306 (2.61%)	
occurrences (all)	2	11	
Platelet count increased			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Prostatic specific antigen increased			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Protein total decreased			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	3	
Protein total increased			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Protein urine present			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
QRS axis abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Red blood cell count increased			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Staphylococcus test positive			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Thyroid function test abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Thyroxine decreased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Thyroxine free decreased			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Visual acuity tests			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Troponin T increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	2 / 304 (0.66%)	14 / 306 (4.58%)	
occurrences (all)	2	16	
Weight increased			
subjects affected / exposed	18 / 304 (5.92%)	8 / 306 (2.61%)	
occurrences (all)	24	10	
White blood cell count			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	2 / 304 (0.66%)	14 / 306 (4.58%)	
occurrences (all)	3	18	
Xanthochromia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Burn oesophageal			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Burn oral cavity			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Chest injury			

subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Contusion			
subjects affected / exposed	2 / 304 (0.66%)	7 / 306 (2.29%)	
occurrences (all)	2	9	
Fall			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Femur fracture			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Incisional hernia			
subjects affected / exposed	7 / 304 (2.30%)	0 / 306 (0.00%)	
occurrences (all)	8	0	
Laceration			
subjects affected / exposed	3 / 304 (0.99%)	1 / 306 (0.33%)	
occurrences (all)	3	1	
Ligament injury			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Patella fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Post procedural complication			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	5 / 304 (1.64%)	2 / 306 (0.65%)	
occurrences (all)	5	2	
Rib fracture			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Skin abrasion			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Skin injury			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Soft tissue injury			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Wound complication			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Wound dehiscence			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 304 (0.33%)	5 / 306 (1.63%)	
occurrences (all)	1	6	
Aortic valve stenosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Arrhythmia			
subjects affected / exposed	5 / 304 (1.64%)	2 / 306 (0.65%)	
occurrences (all)	5	2	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			

subjects affected / exposed	5 / 304 (1.64%)	1 / 306 (0.33%)	
occurrences (all)	5	1	
Bradycardia			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	2	
Bundle branch block left			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cardiac failure			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Cardiovascular disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Conduction disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Diastolic dysfunction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Left ventricular dysfunction			
subjects affected / exposed	3 / 304 (0.99%)	7 / 306 (2.29%)	
occurrences (all)	3	10	
Left ventricular hypertrophy			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Mitral valve prolapse			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Myocardial ischaemia			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Myocarditis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	3 / 304 (0.99%)	1 / 306 (0.33%)	
occurrences (all)	3	1	
Pericardial effusion			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Pericarditis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	2 / 304 (0.66%)	2 / 306 (0.65%)	
occurrences (all)	3	2	
Supraventricular extrasystoles			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Tachycardia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tricuspid valve incompetence			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Ventricular hypokinesia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Carotid arteriosclerosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Carotid artery stenosis			

subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 304 (0.00%)	21 / 306 (6.86%)	
occurrences (all)	0	32	
Aphonia			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Balance disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Cerebral infarction			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Cerebrovascular accident			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Dementia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Depressed level of consciousness			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Disturbance in attention			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	

Dizziness			
subjects affected / exposed	18 / 304 (5.92%)	23 / 306 (7.52%)	
occurrences (all)	22	29	
Dizziness postural			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Dysaesthesia			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	5	
Dysgeusia			
subjects affected / exposed	18 / 304 (5.92%)	103 / 306 (33.66%)	
occurrences (all)	20	163	
Facial nerve disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Facial paralysis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Formication			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Head discomfort			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	36 / 304 (11.84%)	56 / 306 (18.30%)	
occurrences (all)	39	84	
Hyperaesthesia			
subjects affected / exposed	3 / 304 (0.99%)	5 / 306 (1.63%)	
occurrences (all)	3	6	
Hypoaesthesia			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	2	4	
Hypogeusia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	

Hypotonia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	9 / 304 (2.96%)	9 / 306 (2.94%)	
occurrences (all)	12	18	
Loss of consciousness			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	3 / 304 (0.99%)	4 / 306 (1.31%)	
occurrences (all)	4	5	
Migraine			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Muscle contractions involuntary			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Neuropathy peripheral			
subjects affected / exposed	4 / 304 (1.32%)	7 / 306 (2.29%)	
occurrences (all)	5	9	
Paraesthesia			
subjects affected / exposed	11 / 304 (3.62%)	12 / 306 (3.92%)	
occurrences (all)	15	15	
Parkinson’s disease			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 304 (2.30%)	2 / 306 (0.65%)	
occurrences (all)	12	2	

Polyneuropathy			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Presyncope			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Sciatica			
subjects affected / exposed	0 / 304 (0.00%)	6 / 306 (1.96%)	
occurrences (all)	0	6	
Seizure			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Sensory disturbance			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Sensory loss			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Sleep phase rhythm disturbance			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	4	
Tongue paralysis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	3 / 304 (0.99%)	3 / 306 (0.98%)	
occurrences (all)	3	3	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 304 (2.30%)	33 / 306 (10.78%)	
occurrences (all)	8	65	
Eosinopenia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Erythropenia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hyperglobulinaemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Increased tendency to bruise			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	2 / 304 (0.66%)	45 / 306 (14.71%)	
occurrences (all)	3	92	
Lymphadenopathy			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Lymphopenia			
subjects affected / exposed	1 / 304 (0.33%)	8 / 306 (2.61%)	
occurrences (all)	1	14	
Monocytopenia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	2 / 304 (0.66%)	71 / 306 (23.20%)	
occurrences (all)	3	193	
Thrombocytopenia			

subjects affected / exposed	4 / 304 (1.32%)	61 / 306 (19.93%)	
occurrences (all)	8	87	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Deafness unilateral			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Ear discomfort			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
External ear pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	4	
Meniere’s disease			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	5 / 304 (1.64%)	5 / 306 (1.63%)	
occurrences (all)	6	8	
Tympanic membrane perforation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	10 / 304 (3.29%)	7 / 306 (2.29%)	
occurrences (all)	13	15	
Eye disorders			
Blindness unilateral			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Cataract subcapsular			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Diplopia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Dry eye			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	6	
Eye discharge			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Eye haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Eye inflammation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	0 / 304 (0.00%)	5 / 306 (1.63%)	
occurrences (all)	0	6	
Eye oedema			
subjects affected / exposed	0 / 304 (0.00%)	7 / 306 (2.29%)	
occurrences (all)	0	10	
Eye pain			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	2	3	
Eye pruritus			

subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Eye swelling			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	6	
Eyelash discolouration			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Eyelid bleeding			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	1 / 304 (0.33%)	21 / 306 (6.86%)	
occurrences (all)	1	33	
Eyelid pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Glaucoma			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Lacrimal disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Lacrimal gland enlargement			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	1 / 304 (0.33%)	12 / 306 (3.92%)	
occurrences (all)	1	16	
Ocular hyperaemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Ocular surface disease			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Oscillopsia			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Periorbital oedema			
subjects affected / exposed	0 / 304 (0.00%)	7 / 306 (2.29%)	
occurrences (all)	0	15	
Photophobia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Photopsia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Retinopathy hypertensive			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	3 / 304 (0.99%)	2 / 306 (0.65%)	
occurrences (all)	3	2	
Visual acuity reduced			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Visual impairment			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Abdominal discomfort			
subjects affected / exposed	8 / 304 (2.63%)	8 / 306 (2.61%)	
occurrences (all)	8	11	
Abdominal distension			
subjects affected / exposed	4 / 304 (1.32%)	10 / 306 (3.27%)	
occurrences (all)	4	13	
Abdominal hernia			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	

Abdominal pain			
subjects affected / exposed	15 / 304 (4.93%)	42 / 306 (13.73%)	
occurrences (all)	17	70	
Abdominal pain lower			
subjects affected / exposed	1 / 304 (0.33%)	7 / 306 (2.29%)	
occurrences (all)	1	7	
Abdominal pain upper			
subjects affected / exposed	13 / 304 (4.28%)	39 / 306 (12.75%)	
occurrences (all)	15	75	
Abdominal rigidity			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Abdominal tenderness			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Abnormal faeces			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Anal haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	3	
Anal inflammation			
subjects affected / exposed	0 / 304 (0.00%)	6 / 306 (1.96%)	
occurrences (all)	0	7	
Anal pruritus			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	5	
Anal skin tags			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Anorectal discomfort			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	6	

Anorectal disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	2 / 304 (0.66%)	12 / 306 (3.92%)	
occurrences (all)	2	20	
Bowel movement irregularity			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Breath odour			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Change of bowel habit			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Chapped lips			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Colitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Colitis ulcerative			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	32 / 304 (10.53%)	36 / 306 (11.76%)	
occurrences (all)	42	61	
Dental caries			
subjects affected / exposed	0 / 304 (0.00%)	4 / 306 (1.31%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	65 / 304 (21.38%)	174 / 306 (56.86%)	
occurrences (all)	85	458	
Diverticulum intestinal			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	

Dry mouth			
subjects affected / exposed	8 / 304 (2.63%)	14 / 306 (4.58%)	
occurrences (all)	9	18	
Duodenal ulcer			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Duodenitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Duodenogastric reflux			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	6	
Dyspepsia			
subjects affected / exposed	19 / 304 (6.25%)	82 / 306 (26.80%)	
occurrences (all)	23	149	
Dysphagia			
subjects affected / exposed	1 / 304 (0.33%)	15 / 306 (4.90%)	
occurrences (all)	1	24	
Eructation			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	4	
Flatulence			
subjects affected / exposed	14 / 304 (4.61%)	26 / 306 (8.50%)	
occurrences (all)	16	32	
Frequent bowel movements			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Functional gastrointestinal disorder			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	2	
Gastric mucosa erythema			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	4 / 304 (1.32%)	5 / 306 (1.63%)	
occurrences (all)	5	5	

Gastrointestinal disorder			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Gastrointestinal dysplasia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	4	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 304 (2.96%)	27 / 306 (8.82%)	
occurrences (all)	9	40	
Gingival bleeding			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Gingival oedema			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	4	
Gingival pain			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	4	
Gingival recession			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Gingival swelling			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	

Gingival ulceration			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Glossitis			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	5	
Glossodynia			
subjects affected / exposed	0 / 304 (0.00%)	7 / 306 (2.29%)	
occurrences (all)	0	9	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	3 / 304 (0.99%)	12 / 306 (3.92%)	
occurrences (all)	5	18	
Hiatus hernia			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Hyperchlorhydria			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	6	
Hypoaesthesia oral			
subjects affected / exposed	0 / 304 (0.00%)	4 / 306 (1.31%)	
occurrences (all)	0	5	
Impaired gastric emptying			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Inguinal hernia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Large intestine polyp			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Lip disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	

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

Oral mucosal erythema			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	2 / 304 (0.66%)	7 / 306 (2.29%)	
occurrences (all)	2	7	
Oral toxicity			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Palatal oedema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Palatal swelling			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Pancreatic steatosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Perianal erythema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Proctalgia			
subjects affected / exposed	1 / 304 (0.33%)	7 / 306 (2.29%)	
occurrences (all)	1	12	
Proctitis			
subjects affected / exposed	1 / 304 (0.33%)	9 / 306 (2.94%)	
occurrences (all)	1	14	
Rectal haemorrhage			
subjects affected / exposed	1 / 304 (0.33%)	6 / 306 (1.96%)	
occurrences (all)	1	8	
Regurgitation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Salivary hypersecretion			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	

Sensitivity of teeth			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Stomatitis			
subjects affected / exposed	13 / 304 (4.28%)	81 / 306 (26.47%)	
occurrences (all)	17	154	
Swollen tongue			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Tongue disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tongue oedema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tongue ulceration			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Tooth loss			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	3 / 304 (0.99%)	5 / 306 (1.63%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	20 / 304 (6.58%)	55 / 306 (17.97%)	
occurrences (all)	24	98	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 304 (0.33%)	6 / 306 (1.96%)	
occurrences (all)	2	14	
Alopecia			
subjects affected / exposed	2 / 304 (0.66%)	26 / 306 (8.50%)	
occurrences (all)	2	27	
Blister			

subjects affected / exposed	1 / 304 (0.33%)	6 / 306 (1.96%)	
occurrences (all)	1	9	
Cold sweat			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Dermal cyst			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	3 / 304 (0.99%)	5 / 306 (1.63%)	
occurrences (all)	3	6	
Dry skin			
subjects affected / exposed	17 / 304 (5.59%)	43 / 306 (14.05%)	
occurrences (all)	19	59	
Dyshidrotic eczema			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	3 / 304 (0.99%)	5 / 306 (1.63%)	
occurrences (all)	4	8	
Erythema			
subjects affected / exposed	9 / 304 (2.96%)	13 / 306 (4.25%)	
occurrences (all)	12	19	
Erythema multiforme			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Erythrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Exfoliative rash			
subjects affected / exposed	0 / 304 (0.00%)	5 / 306 (1.63%)	
occurrences (all)	0	7	
Granuloma annulare			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hair colour changes			

subjects affected / exposed	7 / 304 (2.30%)	68 / 306 (22.22%)	
occurrences (all)	8	78	
Hair growth abnormal			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Hair texture abnormal			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Hyperhidrosis			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	2	
Hyperkeratosis			
subjects affected / exposed	2 / 304 (0.66%)	10 / 306 (3.27%)	
occurrences (all)	2	13	
Ingrowing nail			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Keloid scar			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Macule			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Nail bed bleeding			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Nail discolouration			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Nail disorder			
subjects affected / exposed	2 / 304 (0.66%)	6 / 306 (1.96%)	
occurrences (all)	2	7	
Nail growth abnormal			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Nail toxicity			

subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	4	
Night sweats			
subjects affected / exposed	2 / 304 (0.66%)	2 / 306 (0.65%)	
occurrences (all)	2	5	
Palmar erythema			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	3	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	31 / 304 (10.20%)	154 / 306 (50.33%)	
occurrences (all)	42	505	
Panniculitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Papule			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 304 (0.00%)	5 / 306 (1.63%)	
occurrences (all)	0	5	
Photosensitivity reaction			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	2	3	
Pigmentation disorder			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Plantar erythema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	21 / 304 (6.91%)	21 / 306 (6.86%)	
occurrences (all)	30	31	
Pruritus generalised			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	4	

Psoriasis			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	29 / 304 (9.54%)	59 / 306 (19.28%)	
occurrences (all)	42	78	
Rash erythematous			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Rash follicular			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Rash generalised			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Rash macular			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	9	
Rash papular			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Rash vesicular			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Scar pain			
subjects affected / exposed	7 / 304 (2.30%)	1 / 306 (0.33%)	
occurrences (all)	8	1	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Skin burning sensation			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	2	
Skin depigmentation			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	

Skin discolouration			
subjects affected / exposed	1 / 304 (0.33%)	24 / 306 (7.84%)	
occurrences (all)	1	27	
Skin disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	0 / 304 (0.00%)	11 / 306 (3.59%)	
occurrences (all)	0	18	
Skin fissures			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	5	
Skin hyperpigmentation			
subjects affected / exposed	2 / 304 (0.66%)	12 / 306 (3.92%)	
occurrences (all)	2	13	
Skin hypertrophy			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Skin hypopigmentation			
subjects affected / exposed	1 / 304 (0.33%)	9 / 306 (2.94%)	
occurrences (all)	1	10	
Skin irritation			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Skin lesion			
subjects affected / exposed	2 / 304 (0.66%)	9 / 306 (2.94%)	
occurrences (all)	2	14	
Skin mass			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Skin odour abnormal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Skin reaction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	

Skin toxicity			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Splinter haemorrhages			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	0 / 304 (0.00%)	5 / 306 (1.63%)	
occurrences (all)	0	13	
Urticaria			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	4	
Urticaria thermal			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Yellow skin			
subjects affected / exposed	2 / 304 (0.66%)	32 / 306 (10.46%)	
occurrences (all)	3	45	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Albuminuria			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Bladder disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Bladder pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Bladder spasm			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Chromaturia			

subjects affected / exposed	0 / 304 (0.00%)	9 / 306 (2.94%)	
occurrences (all)	0	18	
Dysuria			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Haematuria			
subjects affected / exposed	5 / 304 (1.64%)	7 / 306 (2.29%)	
occurrences (all)	6	11	
Nocturia			
subjects affected / exposed	6 / 304 (1.97%)	1 / 306 (0.33%)	
occurrences (all)	6	2	
Pollakiuria			
subjects affected / exposed	3 / 304 (0.99%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Proteinuria			
subjects affected / exposed	9 / 304 (2.96%)	18 / 306 (5.88%)	
occurrences (all)	10	27	
Pyelocaliectasis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Renal cyst			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Renal impairment			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Renal pain			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Urinary incontinence			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Urinary retention			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Urinary tract obstruction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 304 (0.99%)	0 / 306 (0.00%)	
occurrences (all)	3	0	
Breast engorgement			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Endocrine disorders			
Goitre			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Hyperparathyroidism			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hyperthyroidism			
subjects affected / exposed	2 / 304 (0.66%)	12 / 306 (3.92%)	
occurrences (all)	2	13	
Hypothyroidism			
subjects affected / exposed	4 / 304 (1.32%)	56 / 306 (18.30%)	
occurrences (all)	4	72	
Oestrogen deficiency			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Thyroid disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Thyroid mass			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	29 / 304 (9.54%)	35 / 306 (11.44%)	
occurrences (all)	34	52	
Arthritis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	26 / 304 (8.55%)	28 / 306 (9.15%)	
occurrences (all)	29	33	
Bone pain			
subjects affected / exposed	8 / 304 (2.63%)	4 / 306 (1.31%)	
occurrences (all)	8	5	
Bursitis			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Fibromyalgia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Flank pain			
subjects affected / exposed	4 / 304 (1.32%)	3 / 306 (0.98%)	
occurrences (all)	6	3	
Groin pain			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	4	
Haemarthrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Interspinous osteoarthritis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	

Joint swelling			
subjects affected / exposed	2 / 304 (0.66%)	4 / 306 (1.31%)	
occurrences (all)	2	4	
Limb discomfort			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Muscle fatigue			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Muscle mass			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	13 / 304 (4.28%)	25 / 306 (8.17%)	
occurrences (all)	13	30	
Muscular weakness			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 304 (1.32%)	6 / 306 (1.96%)	
occurrences (all)	4	6	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	14 / 304 (4.61%)	13 / 306 (4.25%)	
occurrences (all)	17	16	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	15 / 304 (4.93%)	25 / 306 (8.17%)	
occurrences (all)	15	32	

Myalgia intercostal			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Myositis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	5 / 304 (1.64%)	5 / 306 (1.63%)	
occurrences (all)	5	10	
Nodal osteoarthritis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	3 / 304 (0.99%)	4 / 306 (1.31%)	
occurrences (all)	3	4	
Osteochondrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Osteoporosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Osteoporosis postmenopausal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	20 / 304 (6.58%)	45 / 306 (14.71%)	
occurrences (all)	23	63	
Periarthritis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Rhabdomyolysis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Soft tissue disorder			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	

Spinal column stenosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Spinal pain			
subjects affected / exposed	2 / 304 (0.66%)	8 / 306 (2.61%)	
occurrences (all)	2	9	
Synovial cyst			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Tenosynovitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Dysplastic naevus			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Haemangioma			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	6 / 304 (1.97%)	6 / 306 (1.96%)	
occurrences (all)	6	7	
Bronchitis viral			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Candida infection			

subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	3	
Conjunctivitis			
subjects affected / exposed	4 / 304 (1.32%)	8 / 306 (2.61%)	
occurrences (all)	6	12	
Cystitis			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	3	3	
Diverticulitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	4 / 304 (1.32%)	2 / 306 (0.65%)	
occurrences (all)	4	3	
Enteritis infectious			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Erysipelas			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Folliculitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	3	
Fungal skin infection			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Gastroenteritis			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Gastroenteritis viral			

subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)	
occurrences (all)	2	0	
Genital candidiasis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Genital herpes			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Gingivitis			
subjects affected / exposed	0 / 304 (0.00%)	8 / 306 (2.61%)	
occurrences (all)	0	8	
Helicobacter gastritis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Herpes virus infection			
subjects affected / exposed	1 / 304 (0.33%)	5 / 306 (1.63%)	
occurrences (all)	1	5	
Herpes zoster			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	3 / 304 (0.99%)	6 / 306 (1.96%)	
occurrences (all)	3	7	
Laryngitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Liver abscess			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Localised infection			

subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	3	
Lower respiratory tract infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	20 / 304 (6.58%)	15 / 306 (4.90%)	
occurrences (all)	25	16	
Oral herpes			
subjects affected / exposed	3 / 304 (0.99%)	7 / 306 (2.29%)	
occurrences (all)	4	8	
Oral infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Osteomyelitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Otitis externa			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Periodontitis			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	2	
Peritonsillitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	5 / 304 (1.64%)	6 / 306 (1.96%)	
occurrences (all)	5	6	
Pharyngitis streptococcal			

subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Pilonidal cyst			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Post procedural infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Pulpitis dental			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Retinitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	3 / 304 (0.99%)	7 / 306 (2.29%)	
occurrences (all)	3	7	
Rhinolaryngitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Sinobronchitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	2 / 304 (0.66%)	4 / 306 (1.31%)	
occurrences (all)	2	10	
Skin infection			

subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)		
occurrences (all)	0	2		
Staphylococcal scalded skin syndrome				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Tinea pedis				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Tooth abscess				
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)		
occurrences (all)	0	2		
Tooth infection				
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)		
occurrences (all)	2	4		
Tracheitis				
subjects affected / exposed	2 / 304 (0.66%)	0 / 306 (0.00%)		
occurrences (all)	2	0		
Upper respiratory tract infection				
subjects affected / exposed	5 / 304 (1.64%)	6 / 306 (1.96%)		
occurrences (all)	5	6		
Urinary tract infection				
subjects affected / exposed	7 / 304 (2.30%)	7 / 306 (2.29%)		
occurrences (all)	11	16		
Urogenital infection fungal				
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)		
occurrences (all)	0	1		
Vaginal infection				
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)		
occurrences (all)	1	2		
Viral hepatitis carrier				
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)		
occurrences (all)	1	0		
Viral infection				
subjects affected / exposed	0 / 304 (0.00%)	4 / 306 (1.31%)		
occurrences (all)	0	4		

Viral labyrinthitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Vulvitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 304 (0.33%)	1 / 306 (0.33%)	
occurrences (all)	1	1	
Wound infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	16 / 304 (5.26%)	59 / 306 (19.28%)	
occurrences (all)	20	99	
Diabetes mellitus			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	3	1	
Dyslipidaemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Fluid retention			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	1 / 304 (0.33%)	4 / 306 (1.31%)	
occurrences (all)	1	4	
Hypercalcaemia			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Hypercholesterolaemia			

subjects affected / exposed	7 / 304 (2.30%)	3 / 306 (0.98%)	
occurrences (all)	10	3	
Hypercreatininaemia			
subjects affected / exposed	0 / 304 (0.00%)	2 / 306 (0.65%)	
occurrences (all)	0	3	
Hyperglycaemia			
subjects affected / exposed	11 / 304 (3.62%)	9 / 306 (2.94%)	
occurrences (all)	18	10	
Hyperkalaemia			
subjects affected / exposed	3 / 304 (0.99%)	1 / 306 (0.33%)	
occurrences (all)	3	1	
Hyperlipidaemia			
subjects affected / exposed	1 / 304 (0.33%)	2 / 306 (0.65%)	
occurrences (all)	1	2	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 304 (0.66%)	3 / 306 (0.98%)	
occurrences (all)	2	9	
Hyperuricaemia			
subjects affected / exposed	5 / 304 (1.64%)	4 / 306 (1.31%)	
occurrences (all)	6	7	
Hypoalbuminaemia			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Hypocalcaemia			
subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	3	
Hypoglycaemia			
subjects affected / exposed	3 / 304 (0.99%)	0 / 306 (0.00%)	
occurrences (all)	4	0	
Hypokalaemia			
subjects affected / exposed	0 / 304 (0.00%)	3 / 306 (0.98%)	
occurrences (all)	0	5	
Hypomagnesaemia			
subjects affected / exposed	2 / 304 (0.66%)	1 / 306 (0.33%)	
occurrences (all)	2	1	
Hyponatraemia			

subjects affected / exposed	1 / 304 (0.33%)	3 / 306 (0.98%)	
occurrences (all)	1	6	
Hypophagia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	3 / 304 (0.99%)	7 / 306 (2.29%)	
occurrences (all)	4	14	
Hypoproteinaemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Hypovitaminosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Increased appetite			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 304 (0.33%)	0 / 306 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 304 (0.00%)	1 / 306 (0.33%)	
occurrences (all)	0	1	

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 intrapatient 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 futility 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: