



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
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	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
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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)
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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
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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
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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
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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)
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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 cycle 1/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
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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
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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
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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
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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
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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
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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
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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:	
<p>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.</p>	
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
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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
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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
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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 erythrodysesthesia syndrome	13	0		
Hypertension	6	0		
Asthenia	4	0		
Fatigue	3	1		
Pulmonary embolism	3	1		
Gastroesophageal 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		
Hypertransaminaemia	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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo
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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
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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 occurrences (all)	1 / 304 (0.33%) 1	3 / 306 (0.98%) 4	
Surgical and medical procedures			
Abdominal hernia repair subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Cancer surgery subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Dental implantation subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Hysterectomy subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Injection subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Palatal operation subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Spleen operation subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Therapeutic procedure subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Tooth extraction subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 306 (0.65%) 2	
Wisdom teeth removal subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 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 occurrences (all)	0 / 304 (0.00%) 0	4 / 306 (1.31%) 4	
Therapeutic response unexpected subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 2	
Xerosis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Immune system disorders			
Contrast media allergy subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 6	3 / 306 (0.98%) 3	
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Social circumstances			
Disability subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Walking disability subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Reproductive system and breast disorders			
Amenorrhoea subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 2	
Balanoposthitis subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 306 (0.65%) 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 occurrences (all)	2 / 304 (0.66%) 2	0 / 306 (0.00%) 0	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	1 / 306 (0.33%) 1	
Agitated depression			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 306 (0.00%) 0	
Agitation			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Anger			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Anxiety			
subjects affected / exposed occurrences (all)	14 / 304 (4.61%) 15	10 / 306 (3.27%) 10	
Apathy			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Confusional state			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Depressed mood			
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	3 / 306 (0.98%) 3	
Depression			
subjects affected / exposed occurrences (all)	9 / 304 (2.96%) 9	3 / 306 (0.98%) 5	
Insomnia			
subjects affected / exposed occurrences (all)	19 / 304 (6.25%) 21	30 / 306 (9.80%) 39	
Irritability			
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 5	5 / 306 (1.63%) 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 occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Hepatitis			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Hepatitis acute			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Hepatotoxicity			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Hyperbilirubinaemia			
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 3	5 / 306 (1.63%) 10	
Hypertransaminasaemia			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 306 (0.65%) 3	
Jaundice			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	20 / 306 (6.54%) 22	
Liver disorder			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Portal vein thrombosis			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Investigations			
Alanine aminotransferase			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 306 (0.00%) 0	
Alanine aminotransferase increased			
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	15 / 306 (4.90%) 21	
Amylase increased			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 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 occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Transaminases increased subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 306 (0.65%) 2	
Visual acuity tests subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Troponin T increased subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Weight decreased subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	14 / 306 (4.58%) 16	
Weight increased subjects affected / exposed occurrences (all)	18 / 304 (5.92%) 24	8 / 306 (2.61%) 10	
White blood cell count subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 3	14 / 306 (4.58%) 18	
Xanthochromia subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Injury, poisoning and procedural complications			
Burn oesophageal subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 306 (0.33%) 1	
Burn oral cavity subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 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 occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Skin injury subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Soft tissue injury subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Tibia fracture subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Wound complication subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 306 (0.00%) 0	
Wound dehiscence subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Congenital, familial and genetic disorders Dermoid cyst subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	5 / 306 (1.63%) 6	
Aortic valve stenosis subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Arrhythmia subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 5	2 / 306 (0.65%) 2	
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 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 occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Nervous system disorders			
Ageusia			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	21 / 306 (6.86%) 32	
Aphonia			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 306 (0.33%) 1	
Balance disorder			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Burning sensation			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Carpal tunnel syndrome			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Cerebral infarction			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Cerebrovascular accident			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Cognitive disorder			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Dementia			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Depressed level of consciousness			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Disturbance in attention			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 306 (0.65%) 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 occurrences (all)	4 / 304 (1.32%) 8	61 / 306 (19.93%) 87	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 306 (0.33%) 1	
Deafness unilateral			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 306 (0.00%) 0	
Ear discomfort			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Ear pain			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	3 / 306 (0.98%) 3	
External ear pain			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Hypoacusis			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 306 (0.98%) 4	
Meniere's disease			
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Tinnitus			
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 6	5 / 306 (1.63%) 8	
Tympanic membrane perforation			
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Vertigo			
subjects affected / exposed occurrences (all)	10 / 304 (3.29%) 13	7 / 306 (2.29%) 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 occurrences (all)	1 / 304 (0.33%) 1	2 / 306 (0.65%) 2	
Stomatitis subjects affected / exposed occurrences (all)	13 / 304 (4.28%) 17	81 / 306 (26.47%) 154	
Swollen tongue subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 306 (0.33%) 1	
Tongue disorder subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Tongue oedema subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Tongue ulceration subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	3 / 306 (0.98%) 3	
Tooth loss subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Toothache subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	5 / 306 (1.63%) 5	
Vomiting subjects affected / exposed occurrences (all)	20 / 304 (6.58%) 24	55 / 306 (17.97%) 98	
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	6 / 306 (1.96%) 14	
Alopecia subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	26 / 306 (8.50%) 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 erythrodysesthesia 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 occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 2	
Urinary tract obstruction subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	0 / 306 (0.00%) 0	
Breast engorgement subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Endocrine disorders			
Goitre subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 306 (0.00%) 0	
Hyperparathyroidism subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	12 / 306 (3.92%) 13	
Hypothyroidism subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	56 / 306 (18.30%) 72	
Oestrogen deficiency subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0	
Thyroid disorder subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1	
Thyroid mass subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 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 occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0
Myositis subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1
Neck pain subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 5	5 / 306 (1.63%) 10
Nodal osteoarthritis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0
Osteoarthritis subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	4 / 306 (1.31%) 4
Osteochondrosis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0
Osteoporosis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0
Osteoporosis postmenopausal subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 306 (0.33%) 1
Pain in extremity subjects affected / exposed occurrences (all)	20 / 304 (6.58%) 23	45 / 306 (14.71%) 63
Periarthritis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0
Rhabdomyolysis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 0
Soft tissue disorder subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 306 (0.00%) 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 inpatient sunitinib dose modification. • The timing of the additional MUGA or ECHO assessments was clarified to better correlate the request for testing at 3, 6, and 12 months. • Exclusion criterion 17 and the Life Style Guidelines were modified to reiterate that patients had to agree to continue using adequate contraception for 3 months after the last dose of study treatment. • Additional CYP3A4 inhibitors were added to the concomitant medication section. • Instructions on when additional ECGs were to be performed in the safety assessment section of the protocol were added. • Clarified that this clinical study used the Investigator's Brochure as the reference document for determining expectedness of AEs for regulatory purposes. • Several regulatory agencies required reporting of study results at the end of each clinical study. The definition of "End of Trial" was clarified in this study. The End of Trial was defined as the date of the final data point to be included in the final CSR. • Appendix 1 was updated to included magnesium and urinalysis based on above rationale for revised ECG monitoring and proteinuria monitoring. • Sections 11, 12, and 13 of the protocol were updated based on revised protocol template language for all clinical studies at Pfizer. • Minor administrative changes were made to correct typographical errors, emphasize subtle points or improve internal consistency and clarity of the protocol.

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: