



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 | 07 September 2017 |

Results information

| | |
|--------------------------------|---|
| Result version number | v3 (current) |
| This version publication date | 12 September 2020 |
| First version publication date | 23 March 2017 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Dates of final analysis and global end of trial date need to be corrected |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A6181109 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 April 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 457 |
| From 65 to 84 years | 158 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sunitinib |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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|----------------------------|-----------------------------------|
| Statistical analysis title | DFS- Assessed by the Investigator |
|----------------------------|-----------------------------------|

Statistical analysis description:

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

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

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

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

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

Statistical analyses

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

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

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

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

End point description:

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

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Tolerability Symptoms

| End point title | Number of Subjects With Tolerability Symptoms |
|-----------------|---|
|-----------------|---|

End point description:

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

| End point type | Secondary |
|----------------|-----------|
|----------------|-----------|

End point timeframe:

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

| End point values | Sunitinib | Placebo | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 306 | | |
| Units: Number of subjects | | | | |
| number (not applicable) | | | | |
| Palmar-plantar erythrodysesthesia syndrome | 13 | 0 | | |
| Hypertension | 6 | 0 | | |
| Asthenia | 4 | 0 | | |
| Fatigue | 3 | 1 | | |
| Pulmonary embolism | 3 | 1 | | |
| 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 | | |
| Hypertransaminasaemia | 1 | 0 | | |
| Hypothyroidism | 1 | 0 | | |
| Influenza like illness | 1 | 0 | | |
| Mental status changes | 1 | 0 | | |
| Mucosal inflammation | 1 | 0 | | |
| Myalgia | 1 | 0 | | |
| Myocardial infarction | 1 | 0 | | |
| Myocarditis | 1 | 0 | | |
| Necrosis | 1 | 0 | | |
| Nephrotic syndrome | 1 | 0 | | |
| Neutropenia | 1 | 0 | | |
| Oedema peripheral | 1 | 0 | | |
| Pancytopenia | 1 | 0 | | |
| Post procedural infection | 1 | 0 | | |
| Presyncope | 1 | 0 | | |
| Pyrexia | 1 | 0 | | |
| Stomatitis | 1 | 0 | | |

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Sunitinib |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Testicular swelling | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asphyxia | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cough | | | |
| subjects affected / exposed | 22 / 306 (7.19%) | 20 / 304 (6.58%) | |
| occurrences (all) | 24 | 24 | |
| Dry throat | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 304 (0.66%) | |
| occurrences (all) | 1 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 17 / 306 (5.56%) | 19 / 304 (6.25%) | |
| occurrences (all) | 20 | 23 | |
| Dysphonia | | | |
| subjects affected / exposed | 10 / 306 (3.27%) | 5 / 304 (1.64%) | |
| occurrences (all) | 12 | 5 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 304 (0.33%) | |
| occurrences (all) | 2 | 1 | |
| Epistaxis | | | |

| | | |
|-----------------------------|-------------------|-----------------|
| subjects affected / exposed | 55 / 306 (17.97%) | 9 / 304 (2.96%) |
| occurrences (all) | 92 | 9 |
| Dyspnoea exertional | | |
| subjects affected / exposed | 5 / 306 (1.63%) | 4 / 304 (1.32%) |
| occurrences (all) | 6 | 5 |
| Hiccups | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 3 | 0 |
| Hydrothorax | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Laryngeal pain | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lung disorder | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Lung infiltration | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nasal congestion | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 0 / 304 (0.00%) |
| occurrences (all) | 4 | 0 |
| Nasal discomfort | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Nasal disorder | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 3 | 0 |
| Nasal dryness | | |
| subjects affected / exposed | 5 / 306 (1.63%) | 1 / 304 (0.33%) |
| occurrences (all) | 5 | 1 |
| Nasal inflammation | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oropharyngeal discomfort | | |

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

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

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

| | | | |
|-----------------------------|-----------------|-----------------|--|
| Nervousness | | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 2 / 304 (0.66%) | |
| occurrences (all) | 4 | 2 | |
| Stress | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tension | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) | |
| occurrences (all) | 1 | 1 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) | |
| occurrences (all) | 3 | 1 | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 304 (0.33%) | |
| occurrences (all) | 3 | 1 | |
| Jaundice | | | |

| | | | |
|--------------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 20 / 306 (6.54%) | 0 / 304 (0.00%) | |
| occurrences (all) | 22 | 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 5 / 306 (1.63%) | 2 / 304 (0.66%) | |
| occurrences (all) | 10 | 3 | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Alanine aminotransferase | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Aspartate aminotransferase | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 15 / 306 (4.90%) | 3 / 304 (0.99%) | |
| occurrences (all) | 21 | 3 | |
| Basophil count increased | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 16 / 306 (5.23%) | 2 / 304 (0.66%) | |
| occurrences (all) | 20 | 6 | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood alkaline phosphatase increased | | | |

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

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

| | | |
|---|------------------|-----------------|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Blood thyroid stimulating hormone decreased | | |
| subjects affected / exposed | 6 / 306 (1.96%) | 1 / 304 (0.33%) |
| occurrences (all) | 6 | 1 |
| Blood thyroid stimulating hormone increased | | |
| subjects affected / exposed | 23 / 306 (7.52%) | 7 / 304 (2.30%) |
| occurrences (all) | 28 | 9 |
| Blood triglycerides increased | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 3 |
| Blood urea increased | | |
| subjects affected / exposed | 5 / 306 (1.63%) | 7 / 304 (2.30%) |
| occurrences (all) | 6 | 9 |
| Body temperature increased | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood uric acid increased | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 2 / 304 (0.66%) |
| occurrences (all) | 5 | 2 |
| Cardiac murmur | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 304 (0.66%) |
| occurrences (all) | 0 | 2 |
| Cardiac stress test abnormal | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Chest X-ray abnormal | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Electrocardiogram QT prolonged | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 1 / 304 (0.33%) |
| occurrences (all) | 6 | 7 |
| Electrocardiogram QT interval abnormal | | |

| | | |
|--|-----------------|-----------------|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Ejection fraction decreased | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 6 / 304 (1.97%) |
| occurrences (all) | 3 | 6 |
| Electrocardiogram ST segment depression | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Electrocardiogram ST segment elevation | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Electrocardiogram ST segment abnormal | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Electrocardiogram ST-T change | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 304 (0.66%) |
| occurrences (all) | 1 | 2 |
| Electrocardiogram T wave inversion | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 304 (0.33%) |
| occurrences (all) | 5 | 1 |
| Eosinophil count increased | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 304 (0.66%) |
| occurrences (all) | 0 | 2 |
| Electrocardiogram T wave peaked | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Haemoglobin decreased | | |
| subjects affected / exposed | 9 / 306 (2.94%) | 2 / 304 (0.66%) |
| occurrences (all) | 10 | 4 |
| International normalised ratio increased | | |

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

| | | |
|--------------------------------|-----------------|------------------|
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 304 (0.66%) |
| occurrences (all) | 1 | 2 |
| QRS axis abnormal | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Protein urine present | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Red blood cell count increased | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Thyroid function test abnormal | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Staphylococcus test positive | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Thyroxine decreased | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Thyroxine free decreased | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Transaminases increased | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Troponin T increased | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Visual acuity tests | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Weight increased | | |
| subjects affected / exposed | 8 / 306 (2.61%) | 18 / 304 (5.92%) |
| occurrences (all) | 10 | 24 |
| White blood cell count | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 14 / 306 (4.58%) | 2 / 304 (0.66%) | |
| occurrences (all) | 16 | 2 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 15 / 306 (4.90%) | 2 / 304 (0.66%) | |
| occurrences (all) | 20 | 3 | |
| Xanthochromia | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Urobilinogen urine increased | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Burn oesophageal | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) | |
| occurrences (all) | 1 | 1 | |
| Chest injury | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 304 (0.66%) | |
| occurrences (all) | 0 | 2 | |
| Contusion | | | |
| subjects affected / exposed | 7 / 306 (2.29%) | 2 / 304 (0.66%) | |
| occurrences (all) | 9 | 2 | |
| Burn oral cavity | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 304 (0.66%) | |
| occurrences (all) | 1 | 2 | |
| Incisional hernia | | | |

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

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

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

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

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

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

| | | |
|--|------------------|------------------|
| Muscle contractions involuntary subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Memory impairment subjects affected / exposed | 4 / 306 (1.31%) | 3 / 304 (0.99%) |
| occurrences (all) | 5 | 4 |
| Neuropathy peripheral subjects affected / exposed | 7 / 306 (2.29%) | 4 / 304 (1.32%) |
| occurrences (all) | 9 | 5 |
| Neuralgia subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Parkinson's disease subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Peripheral motor neuropathy subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Paraesthesia subjects affected / exposed | 12 / 306 (3.92%) | 11 / 304 (3.62%) |
| occurrences (all) | 15 | 15 |
| Peripheral sensory neuropathy subjects affected / exposed | 2 / 306 (0.65%) | 7 / 304 (2.30%) |
| occurrences (all) | 2 | 12 |
| Polyneuropathy subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) |
| occurrences (all) | 1 | 1 |
| Presyncope subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Sciatica subjects affected / exposed | 6 / 306 (1.96%) | 0 / 304 (0.00%) |
| occurrences (all) | 6 | 0 |
| Restless legs syndrome subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) |
| occurrences (all) | 1 | 1 |

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

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

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

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| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Eye haemorrhage | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Dry eye | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 1 / 304 (0.33%) |
| occurrences (all) | 6 | 1 |
| Eye discharge | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Eye inflammation | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Eye irritation | | |
| subjects affected / exposed | 5 / 306 (1.63%) | 0 / 304 (0.00%) |
| occurrences (all) | 6 | 0 |
| Eye oedema | | |
| subjects affected / exposed | 7 / 306 (2.29%) | 0 / 304 (0.00%) |
| occurrences (all) | 10 | 0 |
| Eye pain | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 0 / 304 (0.00%) |
| occurrences (all) | 3 | 0 |
| Eye pruritus | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) |
| occurrences (all) | 1 | 1 |
| Eyelash discolouration | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Eye swelling | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 6 | 0 |
| Eyelid oedema | | |
| subjects affected / exposed | 21 / 306 (6.86%) | 1 / 304 (0.33%) |
| occurrences (all) | 33 | 1 |
| Eyelid pain | | |

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

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

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

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

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

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| Gastrointestinal obstruction subjects affected / exposed occurrences (all) | 0 / 306 (0.00%) 0 | 1 / 304 (0.33%) 1 |
| Gastrointestinal pain subjects affected / exposed occurrences (all) | 0 / 306 (0.00%) 0 | 1 / 304 (0.33%) 1 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 27 / 306 (8.82%) 40 | 9 / 304 (2.96%) 9 |
| Gingival oedema subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Gingival bleeding subjects affected / exposed occurrences (all) | 9 / 306 (2.94%) 14 | 0 / 304 (0.00%) 0 |
| Gingival recession subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Gingival swelling subjects affected / exposed occurrences (all) | 2 / 306 (0.65%) 2 | 0 / 304 (0.00%) 0 |
| Gingival pain subjects affected / exposed occurrences (all) | 2 / 306 (0.65%) 3 | 1 / 304 (0.33%) 1 |
| Gingival ulceration subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Glossitis subjects affected / exposed occurrences (all) | 4 / 306 (1.31%) 5 | 1 / 304 (0.33%) 1 |
| Glossodynia subjects affected / exposed occurrences (all) | 4 / 306 (1.31%) 6 | 0 / 304 (0.00%) 0 |
| Haemorrhoids subjects affected / exposed occurrences (all) | 12 / 306 (3.92%) 18 | 3 / 304 (0.99%) 5 |

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| Haemorrhoidal haemorrhage subjects affected / exposed occurrences (all) | 2 / 306 (0.65%) 2 | 0 / 304 (0.00%) 0 |
| Hyperchlorhydria subjects affected / exposed occurrences (all) | 3 / 306 (0.98%) 6 | 0 / 304 (0.00%) 0 |
| Hypoaesthesia oral subjects affected / exposed occurrences (all) | 4 / 306 (1.31%) 5 | 0 / 304 (0.00%) 0 |
| Hiatus hernia subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 1 / 304 (0.33%) 1 |
| Inguinal hernia subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Impaired gastric emptying subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Large intestine polyp subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Lip dry subjects affected / exposed occurrences (all) | 0 / 306 (0.00%) 0 | 1 / 304 (0.33%) 1 |
| Lip disorder subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Loose tooth subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 2 | 0 / 304 (0.00%) 0 |
| Lip ulceration subjects affected / exposed occurrences (all) | 1 / 306 (0.33%) 1 | 0 / 304 (0.00%) 0 |
| Mouth cyst subjects affected / exposed occurrences (all) | 0 / 306 (0.00%) 0 | 1 / 304 (0.33%) 1 |

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

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

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

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

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

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

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| Rash | | |
| subjects affected / exposed | 59 / 306 (19.28%) | 29 / 304 (9.54%) |
| occurrences (all) | 79 | 42 |
| Rash generalised | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Rash papular | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) |
| occurrences (all) | 0 | 1 |
| Rash macular | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 1 / 304 (0.33%) |
| occurrences (all) | 9 | 1 |
| Rash vesicular | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Scar pain | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 7 / 304 (2.30%) |
| occurrences (all) | 1 | 8 |
| Seborrhoeic dermatitis | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Skin burning sensation | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) |
| occurrences (all) | 2 | 1 |
| Skin depigmentation | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 2 | 0 |
| Skin disorder | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Skin discolouration | | |
| subjects affected / exposed | 24 / 306 (7.84%) | 1 / 304 (0.33%) |
| occurrences (all) | 27 | 1 |
| Skin exfoliation | | |
| subjects affected / exposed | 11 / 306 (3.59%) | 0 / 304 (0.00%) |
| occurrences (all) | 18 | 0 |

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

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| Urticaria | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 304 (0.33%) | |
| occurrences (all) | 4 | 1 | |
| Urticaria thermal | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Yellow skin | | | |
| subjects affected / exposed | 33 / 306 (10.78%) | 2 / 304 (0.66%) | |
| occurrences (all) | 46 | 3 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Albuminuria | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Bladder disorder | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Chromaturia | | | |
| subjects affected / exposed | 9 / 306 (2.94%) | 0 / 304 (0.00%) | |
| occurrences (all) | 19 | 0 | |
| Bladder pain | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Bladder spasm | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 304 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Haematuria | | | |
| subjects affected / exposed | 7 / 306 (2.29%) | 5 / 304 (1.64%) | |
| occurrences (all) | 11 | 6 | |
| Nocturia | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 6 / 304 (1.97%) | |
| occurrences (all) | 2 | 6 | |
| Dysuria | | | |

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

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

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

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

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

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

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

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

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

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

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

| | | |
|-----------------------------|-------------------|------------------|
| Decreased appetite | | |
| subjects affected / exposed | 59 / 306 (19.28%) | 16 / 304 (5.26%) |
| occurrences (all) | 99 | 20 |
| Diabetes mellitus | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 304 (0.66%) |
| occurrences (all) | 1 | 3 |
| Fluid retention | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 304 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gout | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 1 / 304 (0.33%) |
| occurrences (all) | 4 | 1 |
| Hypercreatininaemia | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 304 (0.00%) |
| occurrences (all) | 3 | 0 |
| Hypercalcaemia | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 304 (0.33%) |
| occurrences (all) | 1 | 2 |
| Hypercholesterolaemia | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 7 / 304 (2.30%) |
| occurrences (all) | 3 | 10 |
| Hyperkalaemia | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 3 / 304 (0.99%) |
| occurrences (all) | 1 | 3 |
| Hyperlipidaemia | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 304 (0.33%) |
| occurrences (all) | 2 | 1 |
| Hyperglycaemia | | |
| subjects affected / exposed | 9 / 306 (2.94%) | 11 / 304 (3.62%) |
| occurrences (all) | 10 | 18 |
| Hyperuricaemia | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 5 / 304 (1.64%) |
| occurrences (all) | 7 | 6 |
| Hypertriglyceridaemia | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 2 / 304 (0.66%) |
| occurrences (all) | 9 | 2 |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: