



## Clinical trial results:

### A Placebo-Controlled, Double-Blind, Randomized, Multicenter, Three Arm Phase III Trial to Compare the Efficacy and Safety of Ibrutinib vs. Placebo in Previously Untreated Binet Stage A CLL Patients with Risk of Early Disease Progression

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-003211-22 |
| Trial protocol           | DE             |
| Global end of trial date | 11 July 2022   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 24 August 2023 |
| First version publication date | 24 August 2023 |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | CLL12 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |                               |
|------------------------------------|-------------------------------|
| ISRCTN number                      | -                             |
| ClinicalTrials.gov id (NCT number) | NCT02863718                   |
| WHO universal trial number (UTN)   | -                             |
| Other trial identifiers            | Board Approval Number: 13-396 |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Cologne  |
| Sponsor organisation address | Albertus-Magnus-Platz 1, Cologne, Germany, 50923   |
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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                       | 21 December 2022 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 11 July 2022     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 11 July 2022     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate superiority of ibrutinib over placebo in prolonging EFS for subjects with treatment-naïve CLL stage A and intermediate or (very) high risk of disease progression. All subjects with intermediate, (very) high risk randomized to the treatment arm will be treated up to active progressive disease with treatment indication according to iwCLL-Guidelines with the objective to demonstrate prolongation of EFS for the ibrutinib arm. EFS is defined as the time between randomization until active progressive disease with treatment indication according to the iwCLL-Guidelines, initiation of subsequent treatment for CLL, or death.

Protection of trial subjects:

Safety measures to prevent or to manage known risks associated with CLL, such as infections or cytopenia or known adverse reactions related to ibrutinib, such as bleeding events, cardiac arrhythmias and cardiac failure, hypertension and diarrhea have been included in the protocol. In chapter 2.4 of the protocol the most frequent risks were described, including recommendations how to prevent and manage these potential adverse events. The protocol includes sections (section 8.6.) regarding permitted and prohibited medication respectively, known interactions and precautions with concomitant medication, especially with CYP3A4 inhibitors or inducers. The protocol provides clear guidance for dose modifications and treatment discontinuation.

Background therapy:

Asymptomatic patients with early-stage disease (Rai 0, Binet A), should be monitored without therapy unless they have evidence of rapid disease progression. So far, studies on early-stage disease were unable to show a benefit of early therapeutic interventions.

Evidence for comparator:

To date no proven effective intervention for Binet A patients exists and watchful waiting should remain state of the art, especially, because published data do not support the concern, that a "delayed" (start only, when disease progresses to a treatment requiring disease according to the iwCLL guidelines) treatment would lead to a disadvantage of patients in early stage disease. Hence, the use of placebo as the comparator arm was considered justified.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 05 May 2014      |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 8 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 515 |
| Worldwide total number of subjects   | 515          |
| EEA total number of subjects         | 515          |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 313 |
| From 65 to 84 years                       | 201 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

From 5 May 2014 to 14 February 2019, 648 patients consented to participate in the study and were screened for eligibility, of which 133 patients were excluded. A total of 515 patients were enrolled, 152 low-risk patients were allocated to the observational cohort, 182 and 181 patients were randomly assigned to receive ibrutinib and placebo.

### Pre-assignment

Screening details:

From 133 Screening failures, 73 did not meet eligibility criteria, 50 withdrew consent, 4 did not complete risk stratification and 6 were screening failures due to administrative reasons.

### Period 1

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

Blinding implementation details:

The randomization procedure was accomplished by a validated interactive web response system (IWRS). Patients were stratified by TP53 mutation status and risk group. Patients, site staff, and the sponsor's clinical and medical representatives were unaware of treatment group assignments. Ibrutinib and placebo capsules were identical in appearance. The blinding was not broken throughout the study unless it was absolutely considered essential.

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Ibrutinib |

Arm description:

Patients were instructed to take 3 capsules (for a dose of 420 mg Ibrutinib) once daily. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Study drug could be paused for a maximum of 28 consecutive days.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Ibrutinib       |
| Investigational medicinal product code | SUB120863       |
| Other name                             | EU/1/14/945/001 |
| Pharmaceutical forms                   | Capsule, hard   |
| Routes of administration               | Oral use        |

Dosage and administration details:

Ibrutinib 420mg will be administered daily up to active progressive disease with treatment indication according to iwCLL-Guidelines. A cycle is defined as 28 calendar days. Ibrutinib was administered until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was assessed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL Guidelines was observed.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo. A cycle is defined as 28 calendar days. Placebo was continued until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was observed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL guidelines was assessed.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|   |                 |
|---|-----------------|
| Investigational medicinal product name  | Placebo         |
| Investigational medicinal product code  | PL1             |
| Other name  |                 |
| Pharmaceutical forms  | Capsule, hard   |
| Routes of administration  | Oral use        |
| Dosage and administration details:  |                 |
| Placebo to match capsules were also provided as a gray, size 0 hard gelatin capsule for oral administration. Subjects were instructed to take 3 capsules (for a dose of 420 mg), orally once daily. |                 |
| <b>Arm title</b>  | Watch and Wait  |
| Arm description:  |                 |
| Subjects at low risk were not randomized and did not receive treatment but were only followed by watch & wait.  |                 |
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm   |                 |

| <b>Number of subjects in period 1</b>         | Ibrutinib | Placebo | Watch and Wait |
|---|-----------|---------|----------------|
| Started                                       | 182       | 181     | 152            |
| Completed                                     | 64        | 33      | 152            |
| Not completed                                 | 118       | 148     | 0              |
| Any study treatment received                  | 15        | 10      | -              |
| Progressive disease requiring treatment       | 4         | 66      | -              |
| Consent withdrawn by subject                  | 1         | 4       | -              |
| Adverse event, non-fatal                      | 75        | 40      | -              |
| New CLL treatment without progressive disease | 1         | -       | -              |
| Death   | 1         | 1       | -              |
| Non-compliance                                | 12        | 21      | -              |
| Other reason                                  | 9         | 6       | -              |

## Baseline characteristics

### Reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Ibrutinib      |
| Reporting group description:   |                |
| Patients were instructed to take 3 capsules (for a dose of 420 mg Ibrutinib) once daily. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Study drug could be paused for a maximum of 28 consecutive days.   |                |
| Reporting group title  | Placebo        |
| Reporting group description:   |                |
| Subjects received placebo. A cycle is defined as 28 calendar days. Placebo was continued until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was observed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL guidelines was assessed. |                |
| Reporting group title  | Watch and Wait |
| Reporting group description:   |                |
| Subjects at low risk were not randomized and did not receive treatment but were only followed by watch & wait.   |                |

| Reporting group values                             | Ibrutinib | Placebo  | Watch and Wait |
|--|-----------|----------|----------------|
| Number of subjects                                 | 182       | 181      | 152            |
| Age categorical                                    |           |          |                |
| Units: Subjects                                    |           |          |                |
| In utero   | 0         | 0        | 0              |
| Preterm newborn infants (gestational age < 37 wks) | 0         | 0        | 0              |
| Newborns (0-27 days)                               | 0         | 0        | 0              |
| Infants and toddlers (28 days-23 months)           | 0         | 0        | 0              |
| Children (2-11 years)                              | 0         | 0        | 0              |
| Adolescents (12-17 years)                          | 0         | 0        | 0              |
| Adults (18-64 years)                               | 100       | 93       | 120            |
| From 65-84 years                                   | 81        | 88       | 32             |
| 85 years and over                                  | 1         | 0        | 0              |
| Age continuous                                     |           |          |                |
| Units: years                                       |           |          |                |
| median   | 64        | 64       | 57             |
| inter-quartile range (Q1-Q3)                       | 55 to 70  | 55 to 70 | 52 to 63       |
| Gender categorical                                 |           |          |                |
| Units: Subjects                                    |           |          |                |
| Female   | 45        | 54       | 85             |
| Male   | 137       | 127      | 67             |
| GCLLSG Prognostic Index Risk Group                 |           |          |                |
| Units: Subjects                                    |           |          |                |
| low  | 0         | 0        | 152            |
| intermediate                                       | 137       | 136      | 0              |
| high   | 40        | 42       | 0              |
| very high  | 5         | 3        | 0              |
| missing  | 0         | 0        | 0              |
| Binet Stage  |           |          |                |

The Binet staging system is one of the two staging systems currently adopted in assessment of chronic lymphocytic leukemia (CLL). It classifies CLL according to the number of involved regions (spleen, liver and the axillary, cervical and inguinal lymph nodes), as well as the presence of anemia or thrombocytopenia.

|                 |     |     |     |
|-----------------|-----|-----|-----|
| Units: Subjects |     |     |     |
| Binet A         | 181 | 181 | 152 |
| Binet B         | 1   | 0   | 0   |
| Binet C         | 0   | 0   | 0   |

|  |  |  |  |
|--|--|--|--|
| Cytogenetic subgroup by hierarchical order |  |  |  |
|--|--|--|--|

Döhner et al first published a hierarchical model including five categories for chromosomal abnormalities (deletion 17p, deletion 11q, trisomy 12, no abnormalities according to the Döhner's model, deletion 13q) with prognostic value in CLL, with the shortest survival estimates observed in patients with del(17p), followed by those with del(11q) in the absence of del(17p).

|  |    |    |     |
|--|----|----|-----|
| Units: Subjects                              |    |    |     |
| Deletion 17p                                 | 6  | 7  | 0   |
| Deletion 11q                                 | 21 | 19 | 0   |
| Trisomy 12                                   | 24 | 28 | 4   |
| No abnormalities according to Döhner's model | 36 | 30 | 27  |
| Deletion 13q                                 | 95 | 97 | 121 |

|            |  |  |  |
|------------|--|--|--|
| CIRS Score |  |  |  |
|------------|--|--|--|

The Cumulative Illness Rating Scale (CIRS) is a comprehensive tool to evaluate comorbidities, which has been validated in multiple medical settings and is increasingly used in CLL. 14 organ categories can be scored according to the severeness of potential comorbidities with a score between 0 and 4.

|                              |            |            |            |
|------------------------------|------------|------------|------------|
| Units: Score points          |            |            |            |
| median                       | 2          | 3          | 2          |
| inter-quartile range (Q1-Q3) | 1.0 to 4.3 | 1.0 to 4.0 | 0.0 to 3.0 |

|  |       |  |  |
|--|-------|--|--|
| <b>Reporting group values</b>                      | Total |  |  |
| Number of subjects                                 | 515   |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 313   |  |  |
| From 65-84 years                                   | 201   |  |  |
| 85 years and over                                  | 1     |  |  |
| Age continuous                                     |       |  |  |
| Units: years                                       |       |  |  |
| median   |       |  |  |
| inter-quartile range (Q1-Q3)                       | -     |  |  |
| Gender categorical                                 |       |  |  |
| Units: Subjects                                    |       |  |  |
| Female   | 184   |  |  |
| Male   | 331   |  |  |
| GCLLSG Prognostic Index Risk Group                 |       |  |  |
| Units: Subjects                                    |       |  |  |
| low  | 152   |  |  |

|   |     |  |  |
|---|-----|--|--|
| intermediate  | 273 |  |  |
| high  | 82  |  |  |
| very high   | 8   |  |  |
| missing   | 0   |  |  |
| Binet Stage   |     |  |  |
| The Binet staging system is one of the two staging systems currently adopted in assessment of chronic lymphocytic leukemia (CLL). It classifies CLL according to the number of involved regions (spleen, liver and the axillary, cervical and inguinal lymph nodes), as well as the presence of anemia or thrombocytopenia.   |     |  |  |
| Units: Subjects   |     |  |  |
| Binet A   | 514 |  |  |
| Binet B   | 1   |  |  |
| Binet C   | 0   |  |  |
| Cytogenetic subgroup by hierarchical order  |     |  |  |
| Döhner et al first published a hierarchical model including five categories for chromosomal abnormalities (deletion 17p, deletion 11q, trisomy 12, no abnormalities according to the Döhner's model, deletion 13q) with prognostic value in CLL, with the shortest survival estimates observed in patients with del(17p), followed by those with del(11q) in the absence of del(17p). |     |  |  |
| Units: Subjects   |     |  |  |
| Deletion 17p  | 13  |  |  |
| Deletion 11q  | 40  |  |  |
| Trisomy 12  | 56  |  |  |
| No abnormalities according to Doehner's model   | 93  |  |  |
| Deletion 13q  | 313 |  |  |
| CIRS Score  |     |  |  |
| The Cumulative Illness Rating Scale (CIRS) is a comprehensive tool to evaluate comorbidities, which has been validated in multiple medical settings and is increasingly used in CLL. 14 organ categories can be scored according to the severeness of potential comorbidities with a score between 0 and 4.   |     |  |  |
| Units: Score points   |     |  |  |
| median  |     |  |  |
| inter-quartile range (Q1-Q3)  | -   |  |  |



## End points

### End points reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Ibrutinib      |
| Reporting group description:<br>Patients were instructed to take 3 capsules (for a dose of 420 mg Ibrutinib) once daily. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Study drug could be paused for a maximum of 28 consecutive days.   |                |
| Reporting group title  | Placebo        |
| Reporting group description:<br>Subjects received placebo. A cycle is defined as 28 calendar days. Placebo was continued until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was observed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL guidelines was assessed. |                |
| Reporting group title  | Watch and Wait |
| Reporting group description:<br>Subjects at low risk were not randomized and did not receive treatment but were only followed by watch & wait.   |                |

### Primary: Event-free Survival

|  |                                    |
|--|------------------------------------|
| End point title  | Event-free Survival <sup>[1]</sup> |
| End point description:<br>The analysis of the primary efficacy parameter EFS will be performed on the population of all patients with intermediate, high or very high risk being randomized to receive ibrutinib or placebo using a two-sided stratified log-rank test with risk group as stratification factor (intermediate risk / high risk / very high risk) (at 0.05 significance level; not adjusted).<br>In addition Kaplan-Meier survival methodology will be used to calculate the median EFS and estimated EFS rates for one, two and three years etc. after randomization. The corresponding hazard ratio and 95% confidence interval will be determined using a stratified (by risk group) Cox proportional hazard regression model. |                                    |
| End point type   | Primary                            |
| End point timeframe:<br>The primary efficacy parameter is event-free survival (EFS) defined as the time of randomization until symptomatic disease progression with treatment indication, initiation of subsequent treatment for CLL or death by any cause, whichever occurs first.  |                                    |

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary objective of the study is to demonstrate superiority of ibrutinib over placebo in prolonging event-free survival in treatment naïve Binet stage A CLL patients with intermediate to (very) high risk of disease progression. Therefore this analysis was based on randomized patients of the two treatment arms with ibrutinib or placebo.

| End point values            | Ibrutinib          | Placebo         |  |  |
|-----------------------------|--------------------|-----------------|--|--|
| Subject group type          | Reporting group    | Reporting group |  |  |
| Number of subjects analysed | 182 <sup>[2]</sup> | 181             |  |  |
| Units: Percentage           |                    |                 |  |  |
| number (not applicable)     |                    |                 |  |  |
| Median EFS (months)         | 0                  | 51.6            |  |  |
| 1-year survival             | 96.4               | 88.9            |  |  |
| 2-year survival             | 90.9               | 74.5            |  |  |

|                 |      |      |  |  |
|-----------------|------|------|--|--|
| 3-year survival | 87.7 | 61.2 |  |  |
| 4-year survival | 84.1 | 52.2 |  |  |
| 5-year survival | 78.2 | 48.0 |  |  |

Notes:

[2] - Median EFS was not reached in this subgroup.

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Stratified log-rank test regarding EFS |
| Statistical analysis description:  |  |
| Treatment comparison for the primary efficacy parameter EFS will be performed using a two-sided stratified log-rank test using the GCLLSG Prognostic Index Risk Group as stratification factor (at 0.05 significance level; not adjusted). |  |
| Comparison groups  | Ibrutinib v Placebo                    |
| Number of subjects included in analysis  | 363                                    |
| Analysis specification   | Pre-specified                          |
| Analysis type  | superiority                            |
| P-value  | < 0.001                                |
| Method   | log-rank test                          |

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>   | Cox regression regarding EFS |
| Statistical analysis description:   |                              |
| Estimates of the treatment effect will be expressed by the hazard ratio (HR) including the 95% confidence interval estimated through a stratified (by the GCLLSG Prognostic Index Risk Group) Cox proportional hazard regression model. If the null hypothesis is rejected and the observed HR is favorable for the ibrutinib arm, then it is concluded that early treatment with ibrutinib significantly lowers the risk of EFS events in Binet stage A CLL patients with increased risk of disease progression. |                              |
| Comparison groups   | Ibrutinib v Placebo          |
| Number of subjects included in analysis   | 363                          |
| Analysis specification  | Pre-specified                |
| Analysis type   | superiority <sup>[3]</sup>   |
| Parameter estimate  | Cox proportional hazard      |
| Point estimate  | 0.276                        |
| Confidence interval   |                              |
| level   | 95 %                         |
| sides   | 2-sided                      |
| lower limit   | 0.188                        |
| upper limit   | 0.407                        |

Notes:

[3] - In Cox-regression the Placebo-group was used as reference category (Ibrutinib vs. Placebo).

## Secondary: Overall survival

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Overall survival <sup>[4]</sup> |
|-----------------|---------------------------------|

End point description:

The analysis of the secondary efficacy endpoint OS will be performed on the population of all patients with intermediate, high or very high risk being randomized to receive ibrutinib or placebo using a two-sided stratified log-rank test with risk group as stratification factor (intermediate risk / high risk / very high risk).

In addition Kaplan-Meier survival methodology will be used to calculate the median OS and estimated OS rates for one, two and three years etc. after randomization. The corresponding hazard ratio and 95% confidence interval will be determined using a stratified (by risk group) Cox proportional hazard regression model.

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

End point timeframe:

Overall survival (OS) will be calculated from the date of randomization to the date of death due to any cause. Subjects who have not yet died at the time of analysis will be censored at the date of last observation they were assessed to be alive.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The secondary objective of the study is to demonstrate superiority of ibrutinib over placebo in treatment naïve Binet stage A CLL patients with intermediate to (very) high risk of disease progression in prolonging overall survival. Therefore this analysis was based on randomized patients of the two treatment arms with ibrutinib or placebo.

| End point values            | Ibrutinib          | Placebo            |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 182 <sup>[5]</sup> | 181 <sup>[6]</sup> |  |  |
| Units: Percentage           |                    |                    |  |  |
| number (not applicable)     |                    |                    |  |  |
| Median OS                   | 0                  | 0                  |  |  |
| 1-year survival             | 98.8               | 100.0              |  |  |
| 2-year survival             | 97.6               | 100.0              |  |  |
| 3-year survival             | 97.0               | 98.8               |  |  |
| 4-year survival             | 94.1               | 96.0               |  |  |
| 5-year survival             | 93.3               | 93.6               |  |  |

Notes:

[5] - Median OS was not reached in this subgroup.

[6] - Median OS was not reached in this subgroup.

## Statistical analyses

| Statistical analysis title | Stratified log-rank test regarding OS |
|----------------------------|---------------------------------------|
|----------------------------|---------------------------------------|

Statistical analysis description:

Treatment comparison for the secondary efficacy parameter OS will be performed using a two-sided stratified log-rank test using the GCLLSG Prognostic Index Risk Group as stratification factor.

|   |                     |
|---|---------------------|
| Comparison groups                       | Placebo v Ibrutinib |
| Number of subjects included in analysis | 363                 |
| Analysis specification                  | Pre-specified       |
| Analysis type                           | superiority         |
| P-value                                 | = 0.562             |
| Method                                  | log-rank test       |

| Statistical analysis title | Cox regression regarding OS |
|----------------------------|-----------------------------|
|----------------------------|-----------------------------|

Statistical analysis description:

Estimates of the treatment effect will be expressed by the hazard ratio (HR) including the 95% confidence interval estimated through a stratified (by the GCLLSG Prognostic Index Risk Group) Cox proportional hazard regression model.

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Ibrutinib v Placebo |
|-------------------|---------------------|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 363                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[7]</sup> |
| Parameter estimate                      | Cox proportional hazard    |
| Point estimate                          | 0.791                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.358                      |
| upper limit                             | 1.748                      |

Notes:

[7] - In Cox-regression the Placebo-group was used as reference category (Ibrutinib vs. Placebo).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | Ibrutinib |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events  | Placebo  | Ibrutinib          |  |
|---|--|--------------------|--|
| Total subjects affected by serious adverse events                   |  |                    |  |
| subjects affected / exposed   | 101 / 168 (60.12%)                                 | 102 / 170 (60.00%) |  |
| number of deaths (all causes)                                       | 14   | 11                 |  |
| number of deaths resulting from adverse events                      | 13   | 10                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                    |  |
| Adrenal adenoma   | Additional description: Adrenal adenoma            |                    |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0              |  |
| Breast cancer   | Additional description: Breast cancer              |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1  | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0              |  |
| Benign neoplasm of bladder  | Additional description: Benign neoplasm of bladder |                    |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0              |  |
| Basal cell carcinoma  | Additional description: Basal cell carcinoma       |                    |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 12 / 168 (7.14%)  | 4 / 170 (2.35%) |  |
| occurrences causally related to treatment / all | 2 / 18  | 3 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Clear cell renal cell carcinoma                 | Additional description: Clear cell renal cell carcinoma |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Colon adenoma                                   | Additional description: Colon adenoma                   |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Endometrial cancer                              | Additional description: Endometrial cancer              |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastrointestinal stromal tumour                 | Additional description: Gastrointestinal stromal tumour |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Intraductal papilloma of breast                 | Additional description: Intraductal papilloma of breast |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lung adenocarcinoma                             | Additional description: Lung adenocarcinoma             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Lung neoplasm malignant                         | Additional description: Lung neoplasm malignant         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Malignant melanoma                              | Additional description: Malignant melanoma              |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 2 / 168 (1.19%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Meningioma                                      | Additional description: Meningioma                           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Myelodysplastic syndrome                        | Additional description: Myelodysplastic syndrome             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Liposarcoma                                     | Additional description: Liposarcoma                          |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neuroendocrine carcinoma of the skin            | Additional description: Neuroendocrine carcinoma of the skin |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Nodular melanoma                                | Additional description: Nodular melanoma                     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Non-small cell lung cancer                      | Additional description: Non-small cell lung cancer           |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Ovarian adenoma                                 | Additional description: Ovarian adenoma                      |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Ovarian cancer                                  | Additional description: Ovarian cancer                       |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Rectal adenocarcinoma                           | Additional description: Rectal adenocarcinoma           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Prostate cancer                                 | Additional description: Prostate cancer                 |                 |  |
| subjects affected / exposed                     | 5 / 168 (2.98%)   | 4 / 170 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 5   | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Renal cancer metastatic                         | Additional description: Renal cancer metastatic         |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Small cell lung cancer                          | Additional description: Small cell lung cancer          |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Richter's syndrome                              | Additional description: Richter's syndrome              |                 |  |
| subjects affected / exposed                     | 5 / 168 (2.98%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 3   | 0 / 0           |  |
| Thyroid cancer                                  | Additional description: Thyroid cancer                  |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Squamous cell carcinoma                         | Additional description: Squamous cell carcinoma         |                 |  |
| subjects affected / exposed                     | 4 / 168 (2.38%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 1 / 4   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Squamous cell carcinoma of skin                 | Additional description: Squamous cell carcinoma of skin |                 |  |



|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 2 / 168 (1.19%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Uveal melanoma                                  | Additional description: Uveal melanoma                        |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Vascular disorders                              |   |                 |  |
| Circulatory collapse                            | Additional description: Circulatory collapse                  |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hypertension                                    | Additional description: Hypertension                          |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 3 / 170 (1.76%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Haematoma                                       | Additional description: Haematoma                             |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hypertensive crisis                             | Additional description: Hypertensive crisis                   |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Jugular vein distension                         | Additional description: Jugular vein distension               |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Peripheral arterial occlusive disease           | Additional description: Peripheral arterial occlusive disease |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Subdural haemorrhage                            | Additional description: Subdural haemorrhage                  |                 |  |

|  |   |                 |  |
|--|---|-----------------|--|
| subjects affected / exposed                          | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Venous thrombosis limb                               | Additional description: Venous thrombosis limb            |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Surgical and medical procedures                      |   |                 |  |
| Cardiac pacemaker replacement                        | Additional description: Cardiac pacemaker replacement     |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Cardiac resynchronisation therapy                    | Additional description: Cardiac resynchronisation therapy |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Coronary arterial stent insertion                    | Additional description: Coronary arterial stent insertion |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Medical device removal                               | Additional description: Medical device removal            |                 |  |
| subjects affected / exposed                          | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Neuroprosthesis implantation                         | Additional description: Neuroprosthesis implantation      |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Prostatectomy  | Additional description: Prostatectomy                     |                 |  |
| subjects affected / exposed                          | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| General disorders and administration site conditions |   |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Chest pain                                      | Additional description: Chest pain                            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Death   | Additional description: Death                                 |                 |  |
| subjects affected / exposed                     | 4 / 168 (2.38%)   | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 4   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 4   | 0 / 2           |  |
| Hernia  | Additional description: Hernia                                |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| General physical health deterioration           | Additional description: General physical health deterioration |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Necrosis  | Additional description: Necrosis                              |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pyrexia   | Additional description: Pyrexia                               |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Sudden cardiac death                            | Additional description: Sudden cardiac death                  |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Ulcer   | Additional description: Ulcer                                 |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Immune system disorders                         |   |                 |  |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Drug hypersensitivity                           | Additional description: Drug hypersensitivity   |                 |                 |
|   | subjects affected / exposed   | 1 / 168 (0.60%) | 0 / 170 (0.00%) |
|   | occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |
|   | deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        | Additional description: Benign prostatic hyperplasia                                      |                 |                 |
|   | Benign prostatic hyperplasia subjects affected / exposed                                  | 2 / 168 (1.19%) | 2 / 170 (1.18%) |
|   | occurrences causally related to treatment / all   | 0 / 2           | 0 / 2           |
|   | deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |
| Pelvic floor muscle weakness                    | Additional description: Pelvic floor muscle weakness                                      |                 |                 |
|   | subjects affected / exposed   | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|   | occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |
|   | deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |
| Vaginal prolapse                                | Additional description: Vaginal prolapse  |                 |                 |
|   | subjects affected / exposed   | 1 / 168 (0.60%) | 0 / 170 (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 | Additional description: Asthma-chronic obstructive pulmonary disease overlap syndrome     |                 |                 |
|   | Asthma-chronic obstructive pulmonary disease overlap syndrome subjects affected / exposed | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|   | occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |
|   | deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |
| Asthma  | Additional description: Asthma  |                 |                 |
|   | subjects affected / exposed   | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|   | occurrences causally related to treatment / all   | 0 / 0           | 0 / 3           |
|   | deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |
| Dyspnoea  | Additional description: Dyspnoea  |                 |                 |
|   | subjects affected / exposed   | 2 / 168 (1.19%) | 0 / 170 (0.00%) |
|   | occurrences causally related to treatment / all   | 0 / 2           | 0 / 0           |
|   | deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |
| Interstitial lung disease                       | Additional description: Interstitial lung disease   |                 |                 |
|   |   |                 |                 |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Nasal septum deviation                          | Additional description: Nasal septum deviation  |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pleural effusion                                | Additional description: Pleural effusion        |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pulmonary embolism                              | Additional description: Pulmonary embolism      |                 |  |
| subjects affected / exposed                     | 3 / 168 (1.79%)                                 | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Sleep apnoea syndrome                           | Additional description: Sleep apnoea syndrome   |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Psychiatric disorders                           |   |                 |  |
| Delusion of parasitosis                         | Additional description: Delusion of parasitosis |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Depression                                      | Additional description: Depression              |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Investigations                                  |   |                 |  |
| Catheterisation cardiac                         | Additional description: Catheterisation cardiac |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Medical observation                             | Additional description: Medical observation     |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Injury, poisoning and procedural complications  |   |                 |  |
| Ankle fracture                                  | Additional description: Ankle fracture            |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Fractured sacrum                                | Additional description: Fractured sacrum          |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Foot fracture                                   | Additional description: Foot fracture             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Femur fracture                                  | Additional description: Femur fracture            |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Femoral neck fracture                           | Additional description: Femoral neck fracture     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Facial bones fracture                           | Additional description: Facial bones fracture     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Humerus fracture                                | Additional description: Humerus fracture          |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infusion related reaction                       | Additional description: Infusion related reaction |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Joint dislocation                               | Additional description: Joint dislocation         |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Limb fracture                                   | Additional description: Limb fracture             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lumbar vertebral fracture                       | Additional description: Lumbar vertebral fracture |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Meniscus injury                                 | Additional description: Meniscus injury           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Multiple fractures                              | Additional description: Multiple fractures        |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Procedural nausea                               | Additional description: Procedural nausea         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Radius fracture                                 | Additional description: Radius fracture           |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Rib fracture                                    | Additional description: Rib fracture              |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Road traffic accident                           | Additional description: Road traffic accident      |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Skin laceration                                 | Additional description: Skin laceration            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Spinal fracture                                 | Additional description: Spinal fracture            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Splenic rupture                                 | Additional description: Splenic rupture            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Subarachnoid haemorrhage                        | Additional description: Subarachnoid haemorrhage   |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Subdural haematoma                              | Additional description: Subdural haematoma         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 1 / 1           |  |
| Tendon rupture                                  | Additional description: Tendon rupture             |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Toxicity to various agents                      | Additional description: Toxicity to various agents |                 |  |



|   |  |                  |  |
|---|--|------------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Tibia fracture                                  | Additional description: Tibia fracture                   |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Vaccination complication                        | Additional description: Vaccination complication         |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Cardiac disorders                               |  |                  |  |
| Atrial fibrillation                             | Additional description: Atrial fibrillation              |                  |  |
| subjects affected / exposed                     | 3 / 168 (1.79%)  | 11 / 170 (6.47%) |  |
| occurrences causally related to treatment / all | 2 / 4  | 9 / 13           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Arteriosclerosis coronary artery                | Additional description: Arteriosclerosis coronary artery |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Acute myocardial infarction                     | Additional description: Acute myocardial infarction      |                  |  |
| subjects affected / exposed                     | 5 / 168 (2.98%)  | 2 / 170 (1.18%)  |  |
| occurrences causally related to treatment / all | 1 / 5  | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Atrial flutter                                  | Additional description: Atrial flutter                   |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Cardiac arrest                                  | Additional description: Cardiac arrest                   |                  |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 1 / 170 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1            |  |
| Cardiac aneurysm                                | Additional description: Cardiac aneurysm                 |                  |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cardiac disorder                                | Additional description: Cardiac disorder           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cardiac failure congestive                      | Additional description: Cardiac failure congestive |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Chronic coronary syndrome                       | Additional description: Chronic coronary syndrome  |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cardiac failure                                 | Additional description: Cardiac failure            |                 |  |
| subjects affected / exposed                     | 3 / 168 (1.79%)                                    | 3 / 170 (1.76%) |  |
| occurrences causally related to treatment / all | 0 / 4  | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1  | 1 / 1           |  |
| Congestive cardiomyopathy                       | Additional description: Congestive cardiomyopathy  |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Coronary artery disease                         | Additional description: Coronary artery disease    |                 |  |
| subjects affected / exposed                     | 6 / 168 (3.57%)                                    | 6 / 170 (3.53%) |  |
| occurrences causally related to treatment / all | 0 / 6  | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Coronary artery stenosis                        | Additional description: Coronary artery stenosis   |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Mitral valve incompetence                       | Additional description: Mitral valve incompetence  |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Sinus tachycardia                               | Additional description: Sinus tachycardia            |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Tachycardia paroxysmal                          | Additional description: Tachycardia paroxysmal       |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Tricuspid valve incompetence                    | Additional description: Tricuspid valve incompetence |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Ventricular tachycardia                         | Additional description: Ventricular tachycardia      |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Nervous system disorders                        |  |                 |  |
| Basilar artery thrombosis                       | Additional description: Basilar artery thrombosis    |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Basal ganglia infarction                        | Additional description: Basal ganglia infarction     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                      | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Basal ganglia haemorrhage                       | Additional description: Basal ganglia haemorrhage    |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cerebellar infarction                           | Additional description: Cerebellar infarction        |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cerebral haemorrhage                            | Additional description: Cerebral haemorrhage     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cerebral ischaemia                              | Additional description: Cerebral ischaemia       |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cerebrovascular accident                        | Additional description: Cerebrovascular accident |                 |  |
| subjects affected / exposed                     | 3 / 168 (1.79%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cervicobrachial syndrome                        | Additional description: Cervicobrachial syndrome |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Dementia  | Additional description: Dementia                 |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Dizziness                                       | Additional description: Dizziness                |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Dizziness postural                              | Additional description: Dizziness postural       |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Epilepsy  | Additional description: Epilepsy                 |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Embololic stroke                                | Additional description: Embololic stroke                             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Lumbar radiculopathy                            | Additional description: Lumbar radiculopathy                         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neurodegenerative disorder                      | Additional description: Neurodegenerative disorder                   |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Peripheral sensory neuropathy                   | Additional description: Peripheral sensory neuropathy                |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Posterior reversible encephalopathy syndrome    | Additional description: Posterior reversible encephalopathy syndrome |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Radiculopathy                                   | Additional description: Radiculopathy                                |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Sciatica  | Additional description: Sciatica                                     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Seizure   | Additional description: Seizure                                      |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Subarachnoid haemorrhage                        | Additional description: Subarachnoid haemorrhage   |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Syncope   | Additional description: Syncope                    |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Thrombotic stroke                               | Additional description: Thrombotic stroke          |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (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                      | Additional description: Transient ischaemic attack |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Blood and lymphatic system disorders            |  |                 |  |
| Febrile neutropenia                             | Additional description: Febrile neutropenia        |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Haemolytic anaemia                              | Additional description: Haemolytic anaemia         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Haemolysis                                      | Additional description: Haemolysis                 |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Leukocytosis                                    | Additional description: Leukocytosis               |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neutropenia                                     | Additional description: Neutropenia              |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Splenic haematoma                               | Additional description: Splenic haematoma        |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Ear and labyrinth disorders                     |  |                 |  |
| Meniere's disease                               | Additional description: Meniere's disease        |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Vertigo   | Additional description: Vertigo                  |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Eye disorders                                   |  |                 |  |
| Glaucoma  | Additional description: Glaucoma                 |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Retinal artery occlusion                        | Additional description: Retinal artery occlusion |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Retinal degeneration                            | Additional description: Retinal degeneration     |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Retinal haemorrhage                             | Additional description: Retinal haemorrhage      |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastrointestinal disorders                      | Additional description: Abdominal pain                |                 |  |
| Abdominal pain                                  |   |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Colitis ischaemic                               | Additional description: Colitis ischaemic             |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Constipation                                    | Additional description: Constipation                  |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastrointestinal inflammation                   | Additional description: Gastrointestinal inflammation |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hiatus hernia                                   | Additional description: Hiatus hernia                 |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Inguinal hernia                                 | Additional description: Inguinal hernia               |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)                                       | 3 / 170 (1.76%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Large intestinal stenosis                       | Additional description: Large intestinal stenosis     |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Large intestine perforation                     | Additional description: Large intestine perforation   |                 |  |



|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Pancreatitis                                    | Additional description: Pancreatitis        |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Umbilical hernia                                | Additional description: Umbilical hernia    |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                             | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Hepatobiliary disorders                         |   |                 |  |
| Bile duct stone                                 | Additional description: Bile duct stone     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                             | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Cholecystitis acute                             | Additional description: Cholecystitis acute |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                             | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Cholestasis                                     | Additional description: Cholestasis         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Hepatotoxicity                                  | Additional description: Hepatotoxicity      |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Hepatic failure                                 | Additional description: Hepatic failure     |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |   |                 |  |

|                             |   |                 |                 |
|-----------------------------|---|-----------------|-----------------|
| Rash                        | Additional description: Rash                    |                 |                 |
|                             | subjects affected / exposed                     | 1 / 168 (0.60%) | 0 / 170 (0.00%) |
|                             | occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Skin ulcer                  | Additional description: Skin ulcer              |                 |                 |
|                             | subjects affected / exposed                     | 2 / 168 (1.19%) | 0 / 170 (0.00%) |
|                             | occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Renal and urinary disorders |   |                 |                 |
|                             | Additional description: Acute kidney injury     |                 |                 |
|                             | subjects affected / exposed                     | 2 / 168 (1.19%) | 1 / 170 (0.59%) |
|                             | occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |
| Calculus urinary            | Additional description: Calculus urinary        |                 |                 |
|                             | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                             | occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Nephrolithiasis             | Additional description: Nephrolithiasis         |                 |                 |
|                             | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                             | occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Postrenal failure           | Additional description: Postrenal failure       |                 |                 |
|                             | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                             | occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Renal infarct               | Additional description: Renal infarct           |                 |                 |
|                             | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                             | occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Renal colic                 | Additional description: Renal colic             |                 |                 |
|                             | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                             | occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |
|                             | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| Ureteric stenosis           | Additional description: Ureteric stenosis       |                 |                 |
|                             |   |                 |                 |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                              | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Ureterolithiasis                                | Additional description: Ureterolithiasis     |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)                              | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Urethral stenosis                               | Additional description: Urethral stenosis    |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                              | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Urinary incontinence                            | Additional description: Urinary incontinence |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                              | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Endocrine disorders                             |  |                 |  |
| Goitre  | Additional description: Goitre               |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                              | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Thyroid haemorrhage                             | Additional description: Thyroid haemorrhage  |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                              | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |  |                 |  |
| Back pain                                       | Additional description: Back pain            |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                              | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Bursitis  | Additional description: Bursitis             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                              | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |

|  |  |                 |  |
|--|--|-----------------|--|
| Intervertebral disc disorder<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Intervertebral disc disorder   |                 |  |
|  | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
|  | 0 / 1  | 0 / 0           |  |
|  | 0 / 0  | 0 / 0           |  |
| Intervertebral disc protrusion<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Intervertebral disc protrusion |                 |  |
|  | 2 / 168 (1.19%)  | 0 / 170 (0.00%) |  |
|  | 0 / 2  | 0 / 0           |  |
|  | 0 / 0  | 0 / 0           |  |
| Mandibular mass<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                | Additional description: Mandibular mass                |                 |  |
|  | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
|  | 0 / 1  | 0 / 0           |  |
|  | 0 / 0  | 0 / 0           |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all     | Additional description: Musculoskeletal chest pain     |                 |  |
|  | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
|  | 0 / 0  | 1 / 1           |  |
|  | 0 / 0  | 0 / 0           |  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | Additional description: Osteoarthritis                 |                 |  |
|  | 1 / 168 (0.60%)  | 3 / 170 (1.76%) |  |
|  | 0 / 1  | 0 / 4           |  |
|  | 0 / 0  | 0 / 0           |  |
| Osteochondritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                | Additional description: Osteochondritis                |                 |  |
|  | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
|  | 0 / 0  | 0 / 1           |  |
|  | 0 / 0  | 0 / 0           |  |
| Periarthritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | Additional description: Periarthritis                  |                 |  |
|  | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
|  | 0 / 1  | 0 / 0           |  |
|  | 0 / 0  | 0 / 0           |  |
| Rotator cuff syndrome<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all          | Additional description: Rotator cuff syndrome          |                 |  |
|  | 2 / 168 (1.19%)  | 1 / 170 (0.59%) |  |
|  | 0 / 4  | 0 / 1           |  |
|  | 0 / 0  | 0 / 0           |  |
| Spondylolisthesis  | Additional description: Spondylolisthesis              |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Synovial cyst                                   | Additional description: Synovial cyst           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Spinal stenosis                                 | Additional description: Spinal stenosis         |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infections and infestations                     |   |                 |  |
| Appendicitis perforated                         | Additional description: Appendicitis perforated |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Abscess limb                                    | Additional description: Abscess limb            |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Abscess   | Additional description: Abscess                 |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bronchitis                                      | Additional description: Bronchitis              |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bacterial prostatitis                           | Additional description: Bacterial prostatitis   |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Carbuncle                                       | Additional description: Carbuncle               |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bursitis infective                              | Additional description: Bursitis infective            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Clostridium difficile colitis                   | Additional description: Clostridium difficile colitis |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Cellulitis                                      | Additional description: Cellulitis                    |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Clostridium colitis                             | Additional description: Clostridium colitis           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Dacryocystitis                                  | Additional description: Dacryocystitis                |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Device related infection                        | Additional description: Device related infection      |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Diverticulitis                                  | Additional description: Diverticulitis                |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)                                       | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| COVID-19  | Additional description: COVID-19                      |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 7 / 168 (4.17%)                                   | 7 / 170 (4.12%) |  |
| occurrences causally related to treatment / all | 0 / 7   | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| COVID-19 pneumonia                              | Additional description: COVID-19 pneumonia        |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 3 / 170 (1.76%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Cystitis  | Additional description: Cystitis                  |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Cystitis escherichia                            | Additional description: Cystitis escherichia      |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Cytomegalovirus infection                       | Additional description: Cytomegalovirus infection |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastroenteritis                                 | Additional description: Gastroenteritis           |                 |  |
| subjects affected / exposed                     | 3 / 168 (1.79%)                                   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Febrile infection                               | Additional description: Febrile infection         |                 |  |
| subjects affected / exposed                     | 4 / 168 (2.38%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 4   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Escherichia sepsis                              | Additional description: Escherichia sepsis        |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Erysipelas                                      | Additional description: Erysipelas                |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Epididymitis                                    | Additional description: Epididymitis                      |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Embolitic pneumonia                             | Additional description: Embolic pneumonia                 |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Ear infection                                   | Additional description: Ear infection                     |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Herpes zoster meningoencephalitis               | Additional description: Herpes zoster meningoencephalitis |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Herpes zoster                                   | Additional description: Herpes zoster                     |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hepatic cyst infection                          | Additional description: Hepatic cyst infection            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Helicobacter gastritis                          | Additional description: Helicobacter gastritis            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hepatitis E                                     | Additional description: Hepatitis E                       |                 |  |



|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infected dermal cyst                            | Additional description: Infected dermal cyst              |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infection                                       | Additional description: Infection                         |                 |  |
| subjects affected / exposed                     | 2 / 168 (1.19%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 1 / 3   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Influenza                                       | Additional description: Influenza                         |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Injection site abscess                          | Additional description: Injection site abscess            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Intervertebral discitis                         | Additional description: Intervertebral discitis           |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lower respiratory tract infection               | Additional description: Lower respiratory tract infection |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lymphangitis                                    | Additional description: Lymphangitis                      |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Mastoiditis                                     | Additional description: Mastoiditis                       |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neutropenic infection                           | Additional description: Neutropenic infection    |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neutropenic sepsis                              | Additional description: Neutropenic sepsis       |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Oesophageal candidiasis                         | Additional description: Oesophageal candidiasis  |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Ophthalmic herpes zoster                        | Additional description: Ophthalmic herpes zoster |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                  | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Oral herpes                                     | Additional description: Oral herpes              |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Orchitis  | Additional description: Orchitis                 |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Osteomyelitis                                   | Additional description: Osteomyelitis            |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Paronychia                                      | Additional description: Paronychia               |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pericarditis infective                          | Additional description: Pericarditis infective  |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pneumonia                                       | Additional description: Pneumonia               |                 |  |
| subjects affected / exposed                     | 11 / 168 (6.55%)                                | 8 / 170 (4.71%) |  |
| occurrences causally related to treatment / all | 3 / 12  | 7 / 11          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Salmonellosis                                   | Additional description: Salmonellosis           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Sepsis  | Additional description: Sepsis                  |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Staphylococcal sepsis                           | Additional description: Staphylococcal sepsis   |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Urosepsis                                       | Additional description: Urosepsis               |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 2 / 170 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Tonsillitis                                     | Additional description: Tonsillitis             |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Tracheobronchitis viral                         | Additional description: Tracheobronchitis viral |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Upper respiratory tract infection               | Additional description: Upper respiratory tract infection |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Urinary tract infection                         | Additional description: Urinary tract infection           |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 3 / 170 (1.76%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Metabolism and nutrition disorders              |   |                 |  |
| Hyperphosphataemia                              | Additional description: Hyperphosphataemia                |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hyponatraemia                                   | Additional description: Hyponatraemia                     |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Tumour lysis syndrome                           | Additional description: Tumour lysis syndrome             |                 |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Type 2 diabetes mellitus                        | Additional description: Type 2 diabetes mellitus          |                 |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |

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

| Non-serious adverse events  | Placebo                                       | Ibrutinib          |  |
|---|---|--------------------|--|
| Total subjects affected by non-serious adverse events               |   |                    |  |
| subjects affected / exposed   | 164 / 168 (97.62%)                            | 164 / 170 (96.47%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                    |  |
| Adenoma benign  | Additional description: Adenoma benign        |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%)    |  |
| occurrences (all)   | 1   | 0                  |  |
| Angiolipoma   | Additional description: Angiolipoma           |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 1 / 170 (0.59%)    |  |
| occurrences (all)   | 1   | 1                  |  |
| Bowen's disease   | Additional description: Bowen's disease       |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%)    |  |
| occurrences (all)   | 1   | 0                  |  |
| Cancer fatigue  | Additional description: Cancer fatigue        |                    |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)    |  |
| occurrences (all)   | 0   | 1                  |  |
| Colon adenoma   | Additional description: Colon adenoma         |                    |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)    |  |
| occurrences (all)   | 0   | 1                  |  |
| Fibroma   | Additional description: Fibroma               |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%)    |  |
| occurrences (all)   | 1   | 0                  |  |
| Haemangioma of liver  | Additional description: Haemangioma of liver  |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%)    |  |
| occurrences (all)   | 1   | 0                  |  |
| Kidney angiomyolipoma   | Additional description: Kidney angiomyolipoma |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%)    |  |
| occurrences (all)   | 1   | 0                  |  |
| Lipoma  | Additional description: Lipoma                |                    |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                               | 1 / 170 (0.59%)    |  |
| occurrences (all)   | 1   | 1                  |  |
| Melanocytic naevus  | Additional description: Melanocytic naevus    |                    |  |
| subjects affected / exposed   | 2 / 168 (1.19%)                               | 1 / 170 (0.59%)    |  |
| occurrences (all)   | 2   | 2                  |  |
| Seborrhoeic keratosis   | Additional description: Seborrhoeic keratosis |                    |  |

|                             |  |                   |  |
|-----------------------------|--|-------------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                              | 2 / 170 (1.18%)   |  |
| occurrences (all)           | 0  | 2                 |  |
| Skin papilloma              | Additional description: Skin papilloma       |                   |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Sweat gland tumour          | Additional description: Sweat gland tumour   |                   |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Vascular disorders          |  |                   |  |
| Aortic aneurysm             | Additional description: Aortic aneurysm      |                   |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 0 / 170 (0.00%)   |  |
| occurrences (all)           | 1  | 0                 |  |
| Arteriosclerosis            | Additional description: Arteriosclerosis     |                   |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Circulatory collapse        | Additional description: Circulatory collapse |                   |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 2 / 170 (1.18%)   |  |
| occurrences (all)           | 1  | 2                 |  |
| Flushing                    | Additional description: Flushing             |                   |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 2 / 170 (1.18%)   |  |
| occurrences (all)           | 1  | 3                 |  |
| Haematoma                   | Additional description: Haematoma            |                   |  |
| subjects affected / exposed | 9 / 168 (5.36%)                              | 28 / 170 (16.47%) |  |
| occurrences (all)           | 11   | 40                |  |
| Hot flush                   | Additional description: Hot flush            |                   |  |
| subjects affected / exposed | 3 / 168 (1.79%)                              | 2 / 170 (1.18%)   |  |
| occurrences (all)           | 4  | 2                 |  |
| Hypertension                | Additional description: Hypertension         |                   |  |
| subjects affected / exposed | 12 / 168 (7.14%)                             | 28 / 170 (16.47%) |  |
| occurrences (all)           | 12   | 31                |  |
| Hypertensive crisis         | Additional description: Hypertensive crisis  |                   |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 2 / 170 (1.18%)   |  |
| occurrences (all)           | 1  | 3                 |  |
| Hypotension                 | Additional description: Hypotension          |                   |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 0 / 170 (0.00%)   |  |
| occurrences (all)           | 1  | 0                 |  |

|  |   |                 |  |
|--|---|-----------------|--|
| Musculoskeletal and connective tissue disorders<br>subjects affected / exposed<br>occurrences (all)<br><br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)<br><br>Peripheral vascular disorder<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombophlebitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombosis<br>subjects affected / exposed<br>occurrences (all)<br><br>Varicophlebitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Varicose vein<br>subjects affected / exposed<br>occurrences (all) | Additional description: Musculoskeletal and connective tissue disorders |                 |  |
|  | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
|  | 1   | 0               |  |
|  | Additional description: Orthostatic hypotension                         |                 |  |
|  | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
|  | 1   | 0               |  |
|  | Additional description: Peripheral vascular disorder                    |                 |  |
|  | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
|  | 0   | 2               |  |
|  | Additional description: Thrombophlebitis                                |                 |  |
|  | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
|  | 0   | 1               |  |
|  | Additional description: Thrombosis                                      |                 |  |
|  | 2 / 168 (1.19%)   | 0 / 170 (0.00%) |  |
|  | 2   | 0               |  |
|  | Additional description: Varicophlebitis                                 |                 |  |
|  | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
|  | 1   | 0               |  |
|  | Additional description: Varicose vein                                   |                 |  |
|  | 0 / 168 (0.00%)   | 2 / 170 (1.18%) |  |
|  | 0   | 2               |  |
| Surgical and medical procedures<br>Bunion operation<br>subjects affected / exposed<br>occurrences (all)<br><br>Carpal tunnel decompression<br>subjects affected / exposed<br>occurrences (all)<br><br>Dental implantation<br>subjects affected / exposed<br>occurrences (all)<br><br>Dental operation<br>subjects affected / exposed<br>occurrences (all)<br><br>Dental prosthesis placement   |   |                 |  |
|  | Additional description: Bunion operation                                |                 |  |
|  | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
|  | 1   | 0               |  |
|  | Additional description: Carpal tunnel decompression                     |                 |  |
|  | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
|  | 1   | 0               |  |
|  | Additional description: Dental implantation                             |                 |  |
|  | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
|  | 0   | 1               |  |
|  | Additional description: Dental operation                                |                 |  |
|  | 2 / 168 (1.19%)   | 1 / 170 (0.59%) |  |
|  | 2   | 1               |  |
|  | Additional description: Dental prosthesis placement                     |                 |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                          | 1 / 168 (0.60%)                                | 0 / 170 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Foot operation                                       | Additional description: Foot operation         |                 |  |
| subjects affected / exposed                          | 1 / 168 (0.60%)                                | 0 / 170 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Hernia repair  | Additional description: Hernia repair          |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Jaw operation  | Additional description: Jaw operation          |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Inguinal hernia repair                               | Additional description: Inguinal hernia repair |                 |  |
| subjects affected / exposed                          | 1 / 168 (0.60%)                                | 0 / 170 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Lipoma excision                                      | Additional description: Lipoma excision        |                 |  |
| subjects affected / exposed                          | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Renal stone removal                                  | Additional description: Renal stone removal    |                 |  |
| subjects affected / exposed                          | 1 / 168 (0.60%)                                | 0 / 170 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Tooth extraction                                     | Additional description: Tooth extraction       |                 |  |
| subjects affected / exposed                          | 2 / 168 (1.19%)                                | 0 / 170 (0.00%) |  |
| occurrences (all)                                    | 2  | 0               |  |
| General disorders and administration site conditions |  |                 |  |
| Asthenia   | Additional description: Asthenia               |                 |  |
| subjects affected / exposed                          | 1 / 168 (0.60%)                                | 2 / 170 (1.18%) |  |
| occurrences (all)                                    | 1  | 2               |  |
| Axillary pain  | Additional description: Axillary pain          |                 |  |
| subjects affected / exposed                          | 2 / 168 (1.19%)                                | 1 / 170 (0.59%) |  |
| occurrences (all)                                    | 2  | 1               |  |
| Chest pain   | Additional description: Chest pain             |                 |  |
| subjects affected / exposed                          | 7 / 168 (4.17%)                                | 4 / 170 (2.35%) |  |
| occurrences (all)                                    | 8  | 4               |  |
| Chills   | Additional description: Chills                 |                 |  |



|                                       |   |                   |  |
|---------------------------------------|---|-------------------|--|
| subjects affected / exposed           | 2 / 168 (1.19%)   | 3 / 170 (1.76%)   |  |
| occurrences (all)                     | 2   | 3                 |  |
| Discomfort                            | Additional description: Discomfort                            |                   |  |
| subjects affected / exposed           | 1 / 168 (0.60%)   | 1 / 170 (0.59%)   |  |
| occurrences (all)                     | 1   | 1                 |  |
| Fatigue                               | Additional description: Fatigue                               |                   |  |
| subjects affected / exposed           | 35 / 168 (20.83%)   | 47 / 170 (27.65%) |  |
| occurrences (all)                     | 39  | 61                |  |
| Extravasation                         | Additional description: Extravasation                         |                   |  |
| subjects affected / exposed           | 1 / 168 (0.60%)   | 0 / 170 (0.00%)   |  |
| occurrences (all)                     | 1   | 0                 |  |
| Gait disturbance                      | Additional description: Gait disturbance                      |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 1 / 170 (0.59%)   |  |
| occurrences (all)                     | 0   | 1                 |  |
| General physical health deterioration | Additional description: General physical health deterioration |                   |  |
| subjects affected / exposed           | 5 / 168 (2.98%)   | 0 / 170 (0.00%)   |  |
| occurrences (all)                     | 5   | 0                 |  |
| General symptom                       | Additional description: General symptom                       |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 1 / 170 (0.59%)   |  |
| occurrences (all)                     | 0   | 1                 |  |
| Ill-defined disorder                  | Additional description: Ill-defined disorder                  |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 1 / 170 (0.59%)   |  |
| occurrences (all)                     | 0   | 1                 |  |
| Impaired healing                      | Additional description: Impaired healing                      |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 3 / 170 (1.76%)   |  |
| occurrences (all)                     | 0   | 3                 |  |
| Inflammation                          | Additional description: Inflammation                          |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 2 / 170 (1.18%)   |  |
| occurrences (all)                     | 0   | 4                 |  |
| Influenza like illness                | Additional description: Influenza like illness                |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 3 / 170 (1.76%)   |  |
| occurrences (all)                     | 0   | 4                 |  |
| Mucosal inflammation                  | Additional description: Mucosal inflammation                  |                   |  |
| subjects affected / exposed           | 0 / 168 (0.00%)   | 2 / 170 (1.18%)   |  |
| occurrences (all)                     | 0   | 2                 |  |
| Malaise                               | Additional description: Malaise                               |                   |  |

|                              |  |                  |  |
|------------------------------|--|------------------|--|
| subjects affected / exposed  | 2 / 168 (1.19%)                                      | 5 / 170 (2.94%)  |  |
| occurrences (all)            | 2  | 5                |  |
| Oedema                       | Additional description: Oedema                       |                  |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 4 / 170 (2.35%)  |  |
| occurrences (all)            | 1  | 4                |  |
| Oedema peripheral            | Additional description: Oedema peripheral            |                  |  |
| subjects affected / exposed  | 3 / 168 (1.79%)                                      | 12 / 170 (7.06%) |  |
| occurrences (all)            | 3  | 14               |  |
| Performance status decreased | Additional description: Performance status decreased |                  |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%)  |  |
| occurrences (all)            | 1  | 0                |  |
| Pain                         | Additional description: Pain                         |                  |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 4 / 170 (2.35%)  |  |
| occurrences (all)            | 2  | 6                |  |
| Peripheral swelling          | Additional description: Peripheral swelling          |                  |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 5 / 170 (2.94%)  |  |
| occurrences (all)            | 0  | 6                |  |
| Polyp                        | Additional description: Polyp                        |                  |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%)  |  |
| occurrences (all)            | 1  | 0                |  |
| Pyrexia                      | Additional description: Pyrexia                      |                  |  |
| subjects affected / exposed  | 3 / 168 (1.79%)                                      | 7 / 170 (4.12%)  |  |
| occurrences (all)            | 3  | 8                |  |
| Sensation of foreign body    | Additional description: Sensation of foreign body    |                  |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%)  |  |
| occurrences (all)            | 0  | 1                |  |
| Swelling                     | Additional description: Swelling                     |                  |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%)  |  |
| occurrences (all)            | 0  | 1                |  |
| Swelling face                | Additional description: Swelling face                |                  |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%)  |  |
| occurrences (all)            | 1  | 0                |  |
| Temperature intolerance      | Additional description: Temperature intolerance      |                  |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%)  |  |
| occurrences (all)            | 1  | 0                |  |
| Ulcer                        | Additional description: Ulcer                        |                  |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed              | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)                        | 0  | 1               |  |
| Vaccination site reaction                | Additional description: Vaccination site reaction    |                 |  |
| subjects affected / exposed              | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Immune system disorders                  |  |                 |  |
| Allergy to arthropod bite                | Additional description: Allergy to arthropod bite    |                 |  |
| subjects affected / exposed              | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Autoimmune disorder                      | Additional description: Autoimmune disorder          |                 |  |
| subjects affected / exposed              | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)                        | 0  | 1               |  |
| Hypersensitivity                         | Additional description: Hypersensitivity             |                 |  |
| subjects affected / exposed              | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Immunisation reaction                    | Additional description: Immunisation reaction        |                 |  |
| subjects affected / exposed              | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)                        | 0  | 2               |  |
| Seasonal allergy                         | Additional description: Seasonal allergy             |                 |  |
| subjects affected / exposed              | 0 / 168 (0.00%)                                      | 3 / 170 (1.76%) |  |
| occurrences (all)                        | 0  | 4               |  |
| Reproductive system and breast disorders |  |                 |  |
| Balanoposthitis                          | Additional description: Balanoposthitis              |                 |  |
| subjects affected / exposed              | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)                        | 0  | 1               |  |
| Benign prostatic hyperplasia             | Additional description: Benign prostatic hyperplasia |                 |  |
| subjects affected / exposed              | 1 / 168 (0.60%)                                      | 6 / 170 (3.53%) |  |
| occurrences (all)                        | 1  | 6               |  |
| Breast cyst                              | Additional description: Breast cyst                  |                 |  |
| subjects affected / exposed              | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Breast pain                              | Additional description: Breast pain                  |                 |  |
| subjects affected / exposed              | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)                        | 0  | 1               |  |
| Endometrial hyperplasia                  | Additional description: Endometrial hyperplasia      |                 |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Erectile dysfunction        | Additional description: Erectile dysfunction       |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 3 / 170 (1.76%) |  |
| occurrences (all)           | 1  | 3               |  |
| Genital pain                | Additional description: Genital pain               |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Gynaecomastia               | Additional description: Gynaecomastia              |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1  | 1               |  |
| Menopausal symptoms         | Additional description: Menopausal symptoms        |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Metrorrhagia                | Additional description: Metrorrhagia               |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Orchitis noninfective       | Additional description: Orchitis noninfective      |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Postmenopausal haemorrhage  | Additional description: Postmenopausal haemorrhage |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Rectocele                   | Additional description: Rectocele                  |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Prostatitis                 | Additional description: Prostatitis                |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0  | 2               |  |
| Scrotal pain                | Additional description: Scrotal pain               |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 2               |  |
| Testicular pain             | Additional description: Testicular pain            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 3 / 170 (1.76%) |  |
| occurrences (all)           | 0  | 3               |  |
| Vulvovaginal pain           | Additional description: Vulvovaginal pain          |                 |  |

|   |   |                  |  |
|---|---|------------------|--|
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                               | 0   | 1                |  |
| Uterine polyp                                   | Additional description: Uterine polyp                         |                  |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                               | 1   | 0                |  |
| Respiratory, thoracic and mediastinal disorders |   |                  |  |
| Allergic cough                                  | Additional description: Allergic cough                        |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                               | 0   | 1                |  |
| Asthma  | Additional description: Asthma                                |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                               | 0   | 1                |  |
| Bronchitis chronic                              | Additional description: Bronchitis chronic                    |                  |  |
| subjects affected / exposed                     | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                               | 0   | 1                |  |
| Bronchostenosis                                 | Additional description: Bronchostenosis                       |                  |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                               | 1   | 0                |  |
| Chronic obstructive pulmonary disease           | Additional description: Chronic obstructive pulmonary disease |                  |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                               | 1   | 0                |  |
| Cough   | Additional description: Cough                                 |                  |  |
| subjects affected / exposed                     | 13 / 168 (7.74%)  | 14 / 170 (8.24%) |  |
| occurrences (all)                               | 17  | 18               |  |
| Emphysema                                       | Additional description: Emphysema                             |                  |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                               | 1   | 1                |  |
| Dysphonia                                       | Additional description: Dysphonia                             |                  |  |
| subjects affected / exposed                     | 1 / 168 (0.60%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                               | 1   | 1                |  |
| Dyspnoea  | Additional description: Dyspnoea                              |                  |  |
| subjects affected / exposed                     | 9 / 168 (5.36%)   | 10 / 170 (5.88%) |  |
| occurrences (all)                               | 10  | 11               |  |
| Dyspnoea exertional                             | Additional description: Dyspnoea exertional                   |                  |  |

|                               |   |                   |  |
|-------------------------------|---|-------------------|--|
| subjects affected / exposed   | 7 / 168 (4.17%)                                       | 4 / 170 (2.35%)   |  |
| occurrences (all)             | 7   | 5                 |  |
| Epistaxis                     | Additional description: Epistaxis                     |                   |  |
| subjects affected / exposed   | 4 / 168 (2.38%)                                       | 21 / 170 (12.35%) |  |
| occurrences (all)             | 4   | 29                |  |
| Haemoptysis                   | Additional description: Haemoptysis                   |                   |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 2   | 1                 |  |
| Increased bronchial secretion | Additional description: Increased bronchial secretion |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Laryngeal haemorrhage         | Additional description: Laryngeal haemorrhage         |                   |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%)   |  |
| occurrences (all)             | 1   | 0                 |  |
| Lung hypoinflation            | Additional description: Lung hypoinflation            |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Nasal septum deviation        | Additional description: Nasal septum deviation        |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Oropharyngeal discomfort      | Additional description: Oropharyngeal discomfort      |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Oropharyngeal pain            | Additional description: Oropharyngeal pain            |                   |  |
| subjects affected / exposed   | 7 / 168 (4.17%)                                       | 5 / 170 (2.94%)   |  |
| occurrences (all)             | 9   | 7                 |  |
| Pharyngeal oedema             | Additional description: Pharyngeal oedema             |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Pleural effusion              | Additional description: Pleural effusion              |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 3 / 170 (1.76%)   |  |
| occurrences (all)             | 0   | 3                 |  |
| Pulmonary pain                | Additional description: Pulmonary pain                |                   |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Rhinitis allergic             | Additional description: Rhinitis allergic             |                   |  |

|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 1 / 168 (0.60%)                               | 2 / 170 (1.18%) |  |
| occurrences (all)           | 3   | 2               |  |
| Rhinorrhoea                 | Additional description: Rhinorrhoea           |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 4 / 170 (2.35%) |  |
| occurrences (all)           | 1   | 4               |  |
| Sleep apnoea syndrome       | Additional description: Sleep apnoea syndrome |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Throat clearing             | Additional description: Throat clearing       |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Tonsillar hypertrophy       | Additional description: Tonsillar hypertrophy |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Psychiatric disorders       |   |                 |  |
| Agitation                   | Additional description: Agitation             |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 2 / 170 (1.18%) |  |
| occurrences (all)           | 1   | 2               |  |
| Aggression                  | Additional description: Aggression            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Anxiety disorder            | Additional description: Anxiety disorder      |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Anxiety                     | Additional description: Anxiety               |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 2   | 0               |  |
| Aversion                    | Additional description: Aversion              |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Depressed mood              | Additional description: Depressed mood        |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 2   | 0               |  |
| Confusional state           | Additional description: Confusional state     |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |

|                                    |  |                  |
|------------------------------------|--|------------------|
| Depression                         | Additional description: Depression                         |                  |
| subjects affected / exposed        | 4 / 168 (2.38%)  | 3 / 170 (1.76%)  |
| occurrences (all)                  | 4  | 3                |
| Initial insomnia                   | Additional description: Initial insomnia                   |                  |
| subjects affected / exposed        | 1 / 168 (0.60%)  | 0 / 170 (0.00%)  |
| occurrences (all)                  | 1  | 0                |
| Insomnia                           | Additional description: Insomnia                           |                  |
| subjects affected / exposed        | 5 / 168 (2.98%)  | 5 / 170 (2.94%)  |
| occurrences (all)                  | 6  | 5                |
| Libido decreased                   | Additional description: Libido decreased                   |                  |
| subjects affected / exposed        | 1 / 168 (0.60%)  | 0 / 170 (0.00%)  |
| occurrences (all)                  | 1  | 0                |
| Listless                           | Additional description: Listless                           |                  |
| subjects affected / exposed        | 1 / 168 (0.60%)  | 0 / 170 (0.00%)  |
| occurrences (all)                  | 1  | 0                |
| Mood altered                       | Additional description: Mood altered                       |                  |
| subjects affected / exposed        | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |
| occurrences (all)                  | 0  | 1                |
| Nervousness                        | Additional description: Nervousness                        |                  |
| subjects affected / exposed        | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |
| occurrences (all)                  | 0  | 1                |
| Panic attack                       | Additional description: Panic attack                       |                  |
| subjects affected / exposed        | 1 / 168 (0.60%)  | 1 / 170 (0.59%)  |
| occurrences (all)                  | 1  | 1                |
| Psychotic disorder                 | Additional description: Psychotic disorder                 |                  |
| subjects affected / exposed        | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |
| occurrences (all)                  | 0  | 1                |
| Restlessness                       | Additional description: Restlessness                       |                  |
| subjects affected / exposed        | 0 / 168 (0.00%)  | 1 / 170 (0.59%)  |
| occurrences (all)                  | 0  | 1                |
| Sleep disorder                     | Additional description: Sleep disorder                     |                  |
| subjects affected / exposed        | 1 / 168 (0.60%)  | 10 / 170 (5.88%) |
| occurrences (all)                  | 1  | 12               |
| Investigations                     |  |                  |
| Alanine aminotransferase increased | Additional description: Alanine aminotransferase increased |                  |



|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed            | 1 / 168 (0.60%)  | 3 / 170 (1.76%) |  |
| occurrences (all)                      | 1  | 6               |  |
| Arthroscopy                            | Additional description: Arthroscopy                            |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Aspartate aminotransferase increased   | Additional description: Aspartate aminotransferase increased   |                 |  |
| subjects affected / exposed            | 1 / 168 (0.60%)  | 3 / 170 (1.76%) |  |
| occurrences (all)                      | 1  | 4               |  |
| Biopsy prostate                        | Additional description: Biopsy prostate                        |                 |  |
| subjects affected / exposed            | 1 / 168 (0.60%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 1  | 1               |  |
| Blood alkaline phosphatase increased   | Additional description: Blood alkaline phosphatase increased   |                 |  |
| subjects affected / exposed            | 3 / 168 (1.79%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                      | 3  | 0               |  |
| Blood bilirubin increased              | Additional description: Blood bilirubin increased              |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)  | 2 / 170 (1.18%) |  |
| occurrences (all)                      | 0  | 6               |  |
| Blood cholesterol increased            | Additional description: Blood cholesterol increased            |                 |  |
| subjects affected / exposed            | 2 / 168 (1.19%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                      | 2  | 0               |  |
| Blood creatine phosphokinase increased | Additional description: Blood creatine phosphokinase increased |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Blood creatinine increased             | Additional description: Blood creatinine increased             |                 |  |
| subjects affected / exposed            | 2 / 168 (1.19%)  | 3 / 170 (1.76%) |  |
| occurrences (all)                      | 2  | 3               |  |
| Blood glucose increased                | Additional description: Blood glucose increased                |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Blood immunoglobulin G decreased       | Additional description: Blood immunoglobulin G decreased       |                 |  |
| subjects affected / exposed            | 1 / 168 (0.60%)  | 2 / 170 (1.18%) |  |
| occurrences (all)                      | 1  | 2               |  |
| Blood lactate dehydrogenase increased  | Additional description: Blood lactate dehydrogenase increased  |                 |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                  | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                            | 0  | 1               |  |
| Blood potassium decreased                    | Additional description: Blood potassium decreased                    |                 |  |
| subjects affected / exposed                  | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                            | 0  | 2               |  |
| Blood thyroid stimulating hormone increased  | Additional description: Blood thyroid stimulating hormone increased  |                 |  |
| subjects affected / exposed                  | 1 / 168 (0.60%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                            | 1  | 1               |  |
| Blood uric acid increased                    | Additional description: Blood uric acid increased                    |                 |  |
| subjects affected / exposed                  | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                            | 0  | 2               |  |
| Cardiac murmur                               | Additional description: Cardiac murmur                               |                 |  |
| subjects affected / exposed                  | 0 / 168 (0.00%)  | 2 / 170 (1.18%) |  |
| occurrences (all)                            | 0  | 2               |  |
| Blood urea increased                         | Additional description: Blood urea increased                         |                 |  |
| subjects affected / exposed                  | 0 / 168 (0.00%)  | 2 / 170 (1.18%) |  |
| occurrences (all)                            | 0  | 3               |  |
| Electrocardiogram repolarisation abnormality | Additional description: Electrocardiogram repolarisation abnormality |                 |  |
| subjects affected / exposed                  | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                            | 0  | 1               |  |
| Electrocardiogram ST segment depression      | Additional description: Electrocardiogram ST segment depression      |                 |  |
| subjects affected / exposed                  | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                            | 1  | 0               |  |
| Gamma-glutamyltransferase increased          | Additional description: Gamma-glutamyltransferase increased          |                 |  |
| subjects affected / exposed                  | 3 / 168 (1.79%)  | 3 / 170 (1.76%) |  |
| occurrences (all)                            | 3  | 4               |  |
| Hepatic enzyme increased                     | Additional description: Hepatic enzyme increased                     |                 |  |
| subjects affected / exposed                  | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                            | 1  | 0               |  |
| Heart rate irregular                         | Additional description: Heart rate irregular                         |                 |  |
| subjects affected / exposed                  | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                            | 1  | 0               |  |
| Immunoglobulins decreased                    | Additional description: Immunoglobulins decreased                    |                 |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                    | 2 / 168 (1.19%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                              | 2  | 0               |  |
| Lipase increased                               | Additional description: Lipase increased                     |                 |  |
| subjects affected / exposed                    | 0 / 168 (0.00%)  | 2 / 170 (1.18%) |  |
| occurrences (all)                              | 0  | 2               |  |
| Prostatic specific antigen increased           | Additional description: Prostatic specific antigen increased |                 |  |
| subjects affected / exposed                    | 0 / 168 (0.00%)  | 2 / 170 (1.18%) |  |
| occurrences (all)                              | 0  | 2               |  |
| Smear cervix                                   | Additional description: Smear cervix                         |                 |  |
| subjects affected / exposed                    | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Transaminases increased                        | Additional description: Transaminases increased              |                 |  |
| subjects affected / exposed                    | 0 / 168 (0.00%)  | 3 / 170 (1.76%) |  |
| occurrences (all)                              | 0  | 4               |  |
| Urine uric acid increased                      | Additional description: Urine uric acid increased            |                 |  |
| subjects affected / exposed                    | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                              | 0  | 1               |  |
| Weight increased                               | Additional description: Weight increased                     |                 |  |
| subjects affected / exposed                    | 0 / 168 (0.00%)  | 3 / 170 (1.76%) |  |
| occurrences (all)                              | 0  | 3               |  |
| Weight decreased                               | Additional description: Weight decreased                     |                 |  |
| subjects affected / exposed                    | 3 / 168 (1.79%)  | 4 / 170 (2.35%) |  |
| occurrences (all)                              | 4  | 4               |  |
| Injury, poisoning and procedural complications |  |                 |  |
| Acetabulum fracture                            | Additional description: Acetabulum fracture                  |                 |  |
| subjects affected / exposed                    | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Accident at work                               | Additional description: Accident at work                     |                 |  |
| subjects affected / exposed                    | 1 / 168 (0.60%)  | 0 / 170 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Animal scratch                                 | Additional description: Animal scratch                       |                 |  |
| subjects affected / exposed                    | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |  |
| occurrences (all)                              | 0  | 1               |  |
| Ankle fracture                                 | Additional description: Ankle fracture                       |                 |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                          | 3 / 170 (1.76%) |  |
| occurrences (all)           | 0  | 3               |  |
| Arthropod bite              | Additional description: Arthropod bite   |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                          | 4 / 170 (2.35%) |  |
| occurrences (all)           | 2  | 7               |  |
| Arthropod sting             | Additional description: Arthropod sting  |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                          | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Bone contusion              | Additional description: Bone contusion   |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                          | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Burn oral cavity            | Additional description: Burn oral cavity |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                          | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Cartilage injury            | Additional description: Cartilage injury |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                          | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Concussion                  | Additional description: Concussion       |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                          | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Contusion                   | Additional description: Contusion        |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                          | 8 / 170 (4.71%) |  |
| occurrences (all)           | 2  | 10              |  |
| Fall                        | Additional description: Fall             |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                          | 2 / 170 (1.18%) |  |
| occurrences (all)           | 2  | 2               |  |
| Foot fracture               | Additional description: Foot fracture    |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                          | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1  | 1               |  |
| Fracture                    | Additional description: Fracture         |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                          | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Hand fracture               | Additional description: Hand fracture    |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                          | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Ilium fracture              | Additional description: Ilium fracture   |                 |  |

|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Joint injury                | Additional description: Joint injury              |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Infusion related reaction   | Additional description: Infusion related reaction |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                   | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Injury corneal              | Additional description: Injury corneal            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Laceration                  | Additional description: Laceration                |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                   | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Ligament rupture            | Additional description: Ligament rupture          |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                   | 4 / 170 (2.35%) |  |
| occurrences (all)           | 0   | 4               |  |
| Ligament sprain             | Additional description: Ligament sprain           |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Limb injury                 | Additional description: Limb injury               |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                   | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Lumbar vertebral fracture   | Additional description: Lumbar vertebral fracture |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                   | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Muscle rupture              | Additional description: Muscle rupture            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                   | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Meniscus injury             | Additional description: Meniscus injury           |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                                   | 2 / 170 (1.18%) |  |
| occurrences (all)           | 2   | 2               |  |
| Muscle strain               | Additional description: Muscle strain             |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                   | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Nail avulsion               | Additional description: Nail avulsion             |                 |  |

|                                  |   |                 |  |
|----------------------------------|---|-----------------|--|
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Patella fracture                 | Additional description: Patella fracture            |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Post-traumatic pain              | Additional description: Post-traumatic pain         |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Skin laceration                  | Additional description: Skin laceration             |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Spinal compression fracture      | Additional description: Spinal compression fracture |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Spinal fracture                  | Additional description: Spinal fracture             |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Skin abrasion                    | Additional description: Skin abrasion               |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Sunburn                          | Additional description: Sunburn                     |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Traumatic fracture               | Additional description: Traumatic fracture          |                 |  |
| subjects affected / exposed      | 1 / 168 (0.60%)                                     | 0 / 170 (0.00%) |  |
| occurrences (all)                | 1   | 0               |  |
| Traumatic haematoma              | Additional description: Traumatic haematoma         |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 2 / 170 (1.18%) |  |
| occurrences (all)                | 0   | 3               |  |
| Wound complication               | Additional description: Wound complication          |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%) |  |
| occurrences (all)                | 0   | 1               |  |
| Wound                            | Additional description: Wound                       |                 |  |
| subjects affected / exposed      | 0 / 168 (0.00%)                                     | 2 / 170 (1.18%) |  |
| occurrences (all)                | 0   | 2               |  |
| Congenital, familial and genetic |   |                 |  |

|   |   |                  |  |
|---|---|------------------|--|
| disorders                               |   |                  |  |
| Atrial septal defect                    | Additional description: Atrial septal defect                    |                  |  |
| subjects affected / exposed             | 1 / 168 (0.60%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                       | 1   | 0                |  |
| Factor V Leiden mutation                | Additional description: Factor V Leiden mutation                |                  |  |
| subjects affected / exposed             | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                       | 0   | 1                |  |
| Hereditary motor and sensory neuropathy | Additional description: Hereditary motor and sensory neuropathy |                  |  |
| subjects affected / exposed             | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                       | 0   | 1                |  |
| Hydrocele                               | Additional description: Hydrocele                               |                  |  |
| subjects affected / exposed             | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                       | 0   | 1                |  |
| Phimosis                                | Additional description: Phimosis                                |                  |  |
| subjects affected / exposed             | 1 / 168 (0.60%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                       | 1   | 0                |  |
| Cardiac disorders                       |   |                  |  |
| Acute myocardial infarction             | Additional description: Acute myocardial infarction             |                  |  |
| subjects affected / exposed             | 2 / 168 (1.19%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                       | 2   | 0                |  |
| Angina pectoris                         | Additional description: Angina pectoris                         |                  |  |
| subjects affected / exposed             | 2 / 168 (1.19%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                       | 2   | 1                |  |
| Aortic valve incompetence               | Additional description: Aortic valve incompetence               |                  |  |
| subjects affected / exposed             | 1 / 168 (0.60%)   | 0 / 170 (0.00%)  |  |
| occurrences (all)                       | 1   | 0                |  |
| Arrhythmia                              | Additional description: Arrhythmia                              |                  |  |
| subjects affected / exposed             | 1 / 168 (0.60%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                       | 1   | 1                |  |
| Arteriosclerosis coronary artery        | Additional description: Arteriosclerosis coronary artery        |                  |  |
| subjects affected / exposed             | 0 / 168 (0.00%)   | 1 / 170 (0.59%)  |  |
| occurrences (all)                       | 0   | 1                |  |
| Atrial fibrillation                     | Additional description: Atrial fibrillation                     |                  |  |
| subjects affected / exposed             | 2 / 168 (1.19%)   | 16 / 170 (9.41%) |  |
| occurrences (all)                       | 9   | 16               |  |
| Atrioventricular block first degree     | Additional description: Atrioventricular block first degree     |                  |  |

|                              |  |                 |  |
|------------------------------|--|-----------------|--|
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Cardiovascular disorder      | Additional description: Cardiovascular disorder      |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 1  | 6               |  |
| Bradycardia                  | Additional description: Bradycardia                  |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 2 / 170 (1.18%) |  |
| occurrences (all)            | 0  | 2               |  |
| Cardiac failure              | Additional description: Cardiac failure              |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Cardiomegaly                 | Additional description: Cardiomegaly                 |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 1               |  |
| Coronary artery disease      | Additional description: Coronary artery disease      |                 |  |
| subjects affected / exposed  | 3 / 168 (1.79%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 3  | 1               |  |
| Coronary artery stenosis     | Additional description: Coronary artery stenosis     |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 2  | 0               |  |
| Extrasystoles                | Additional description: Extrasystoles                |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 2               |  |
| Hypertensive heart disease   | Additional description: Hypertensive heart disease   |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 1  | 1               |  |
| Left ventricular hypertrophy | Additional description: Left ventricular hypertrophy |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 1               |  |
| Mitral valve incompetence    | Additional description: Mitral valve incompetence    |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 1  | 1               |  |
| Palpitations                 | Additional description: Palpitations                 |                 |  |
| subjects affected / exposed  | 5 / 168 (2.98%)                                      | 3 / 170 (1.76%) |  |
| occurrences (all)            | 6  | 4               |  |
| Pericardial effusion         | Additional description: Pericardial effusion         |                 |  |



|                              |  |                 |  |
|------------------------------|--|-----------------|--|
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Sinus tachycardia            | Additional description: Sinus tachycardia            |                 |  |
| subjects affected / exposed  | 2 / 168 (1.19%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 2  | 0               |  |
| Sinus bradycardia            | Additional description: Sinus bradycardia            |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 1               |  |
| Tachyarrhythmia              | Additional description: Tachyarrhythmia              |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 1               |  |
| Tachycardia                  | Additional description: Tachycardia                  |                 |  |
| subjects affected / exposed  | 4 / 168 (2.38%)                                      | 5 / 170 (2.94%) |  |
| occurrences (all)            | 4  | 5               |  |
| Tricuspid valve incompetence | Additional description: Tricuspid valve incompetence |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Ventricular extrasystoles    | Additional description: Ventricular extrasystoles    |                 |  |
| subjects affected / exposed  | 2 / 168 (1.19%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 2  | 1               |  |
| Nervous system disorders     |  |                 |  |
| Ageusia                      | Additional description: Ageusia                      |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 1               |  |
| Balance disorder             | Additional description: Balance disorder             |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 2 / 170 (1.18%) |  |
| occurrences (all)            | 0  | 2               |  |
| Basilar migraine             | Additional description: Basilar migraine             |                 |  |
| subjects affected / exposed  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |  |
| occurrences (all)            | 0  | 1               |  |
| Cognitive disorder           | Additional description: Cognitive disorder           |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Carotid artery stenosis      | Additional description: Carotid artery stenosis      |                 |  |
| subjects affected / exposed  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |

|  |  |                         |
|--|--|-------------------------|
| Carpal tunnel syndrome<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Carpal tunnel syndrome   |                         |
|  | 1 / 168 (0.60%)<br>1                             | 1 / 170 (0.59%)<br>1    |
| Cervical syndrome<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Cervical syndrome        |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1    |
| Cervicobrachial syndrome<br>subjects affected / exposed<br>occurrences (all) | Additional description: Cervicobrachial syndrome |                         |
|  | 0 / 168 (0.00%)<br>0                             | 2 / 170 (1.18%)<br>2    |
| Convulsion<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Convulsion               |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1    |
| Dementia<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Dementia                 |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Dizziness                |                         |
|  | 11 / 168 (6.55%)<br>13                           | 26 / 170 (15.29%)<br>41 |
| Diabetic neuropathy<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Diabetic neuropathy      |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1    |
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all) | Additional description: Disturbance in attention |                         |
|  | 0 / 168 (0.00%)<br>0                             | 2 / 170 (1.18%)<br>3    |
| Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Dysaesthesia             |                         |
|  | 1 / 168 (0.60%)<br>1                             | 2 / 170 (1.18%)<br>2    |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Dysgeusia                |                         |
|  | 0 / 168 (0.00%)<br>0                             | 2 / 170 (1.18%)<br>2    |
| Headache<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Headache                 |                         |
|  | 20 / 168 (11.90%)<br>39                          | 30 / 170 (17.65%)<br>48 |
| Hypertonia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Hypertonia               |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1    |

|   |   |                       |
|---|---|-----------------------|
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Hypoaesthesia         |                       |
|   | 1 / 168 (0.60%)<br>1                          | 4 / 170 (2.35%)<br>4  |
| Hypoaesthesia oral<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Hypoaesthesia oral    |                       |
|   | 1 / 168 (0.60%)<br>1                          | 0 / 170 (0.00%)<br>0  |
| Intercostal neuralgia<br>subjects affected / exposed<br>occurrences (all) | Additional description: Intercostal neuralgia |                       |
|   | 1 / 168 (0.60%)<br>1                          | 0 / 170 (0.00%)<br>0  |
| Loss of consciousness<br>subjects affected / exposed<br>occurrences (all) | Additional description: Loss of consciousness |                       |
|   | 0 / 168 (0.00%)<br>0                          | 2 / 170 (1.18%)<br>2  |
| Muscle spasticity<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Muscle spasticity     |                       |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1  |
| Memory impairment<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Memory impairment     |                       |
|   | 1 / 168 (0.60%)<br>1                          | 1 / 170 (0.59%)<br>1  |
| Migraine<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Migraine              |                       |
|   | 2 / 168 (1.19%)<br>3                          | 1 / 170 (0.59%)<br>1  |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Neuralgia             |                       |
|   | 1 / 168 (0.60%)<br>1                          | 2 / 170 (1.18%)<br>2  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | Additional description: Neuropathy peripheral |                       |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Paraesthesia          |                       |
|   | 1 / 168 (0.60%)<br>1                          | 8 / 170 (4.71%)<br>12 |
| Paraparesis<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Paraparesis           |                       |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1  |
| Parkinson's disease<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Parkinson's disease   |                       |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1  |

|                                      |   |                 |                 |
|--------------------------------------|---|-----------------|-----------------|
| Parosmia                             | Additional description: Parosmia                |                 |                 |
|                                      | subjects affected / exposed                     | 2 / 168 (1.19%) | 0 / 170 (0.00%) |
|                                      | occurrences (all)                               | 2               | 0               |
| Polyneuropathy                       | Additional description: Polyneuropathy          |                 |                 |
|                                      | subjects affected / exposed                     | 2 / 168 (1.19%) | 6 / 170 (3.53%) |
|                                      | occurrences (all)                               | 2               | 6               |
| Radiculopathy                        | Additional description: Radiculopathy           |                 |                 |
|                                      | subjects affected / exposed                     | 1 / 168 (0.60%) | 0 / 170 (0.00%) |
|                                      | occurrences (all)                               | 1               | 0               |
| Sciatica                             | Additional description: Sciatica                |                 |                 |
|                                      | subjects affected / exposed                     | 1 / 168 (0.60%) | 2 / 170 (1.18%) |
|                                      | occurrences (all)                               | 1               | 2               |
| Syncope                              | Additional description: Syncope                 |                 |                 |
|                                      | subjects affected / exposed                     | 0 / 168 (0.00%) | 3 / 170 (1.76%) |
|                                      | occurrences (all)                               | 0               | 3               |
| Tremor                               | Additional description: Tremor                  |                 |                 |
|                                      | subjects affected / exposed                     | 1 / 168 (0.60%) | 1 / 170 (0.59%) |
|                                      | occurrences (all)                               | 1               | 1               |
| Vascular encephalopathy              | Additional description: Vascular encephalopathy |                 |                 |
|                                      | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                                      | occurrences (all)                               | 0               | 1               |
| Blood and lymphatic system disorders |   |                 |                 |
| Anaemia                              | Additional description: Anaemia                 |                 |                 |
|                                      | subjects affected / exposed                     | 4 / 168 (2.38%) | 4 / 170 (2.35%) |
|                                      | occurrences (all)                               | 4               | 4               |
| Coagulopathy                         | Additional description: Coagulopathy            |                 |                 |
|                                      | subjects affected / exposed                     | 1 / 168 (0.60%) | 0 / 170 (0.00%) |
|                                      | occurrences (all)                               | 1               | 0               |
| Eosinophilia                         | Additional description: Eosinophilia            |                 |                 |
|                                      | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                                      | occurrences (all)                               | 0               | 1               |
| Haemorrhagic diathesis               | Additional description: Haemorrhagic diathesis  |                 |                 |
|                                      | subjects affected / exposed                     | 0 / 168 (0.00%) | 1 / 170 (0.59%) |
|                                      | occurrences (all)                               | 0               | 1               |
| Immune thrombocytopenia              | Additional description: Immune thrombocytopenia |                 |                 |
|                                      |   |                 |                 |

|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Iron deficiency anaemia     | Additional description: Iron deficiency anaemia |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Leukocytosis                | Additional description: Leukocytosis            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Lymph node pain             | Additional description: Lymph node pain         |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Lymphadenopathy             | Additional description: Lymphadenopathy         |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Neutropenia                 | Additional description: Neutropenia             |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                 | 2 / 170 (1.18%) |  |
| occurrences (all)           | 1   | 3               |  |
| Splenomegaly                | Additional description: Splenomegaly            |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Thrombocytopenia            | Additional description: Thrombocytopenia        |                 |  |
| subjects affected / exposed | 3 / 168 (1.79%)                                 | 5 / 170 (2.94%) |  |
| occurrences (all)           | 4   | 5               |  |
| Ear and labyrinth disorders |   |                 |  |
| Ear disorder                | Additional description: Ear disorder            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Ear discomfort              | Additional description: Ear discomfort          |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Ear pain                    | Additional description: Ear pain                |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                 | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Ear pruritus                | Additional description: Ear pruritus            |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |

|  |  |                  |  |
|--|--|------------------|--|
| Ear swelling<br>subjects affected / exposed<br>occurrences (all)<br><br>Ear haemorrhage<br>subjects affected / exposed<br>occurrences (all)<br><br>Hyperacusis<br>subjects affected / exposed<br>occurrences (all)<br><br>Sudden hearing loss<br>subjects affected / exposed<br>occurrences (all)<br><br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)<br><br>Vertigo<br>subjects affected / exposed<br>occurrences (all)<br><br>Vertigo positional<br>subjects affected / exposed<br>occurrences (all) | Additional description: Ear swelling             |                  |  |
|  | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%)  |  |
|  | 1  | 0                |  |
|  | Additional description: Ear haemorrhage          |                  |  |
|  | 1 / 168 (0.60%)                                  | 0 / 170 (0.00%)  |  |
|  | 1  | 0                |  |
|  | Additional description: Hyperacusis              |                  |  |
|  | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%)  |  |
|  | 0  | 1                |  |
|  | Additional description: Sudden hearing loss      |                  |  |
|  | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%)  |  |
|  | 0  | 1                |  |
|  | Additional description: Tinnitus                 |                  |  |
|  | 2 / 168 (1.19%)                                  | 1 / 170 (0.59%)  |  |
|  | 2  | 1                |  |
|  | Additional description: Vertigo                  |                  |  |
|  | 8 / 168 (4.76%)                                  | 12 / 170 (7.06%) |  |
|  | 8  | 17               |  |
|  | Additional description: Vertigo positional       |                  |  |
|  | 1 / 168 (0.60%)                                  | 1 / 170 (0.59%)  |  |
|  | 1  | 1                |  |
| Eye disorders<br>Blepharitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Blepharospasm<br>subjects affected / exposed<br>occurrences (all)<br><br>Blindness<br>subjects affected / exposed<br>occurrences (all)<br><br>Cataract<br>subjects affected / exposed<br>occurrences (all)<br><br>Conjunctival haemorrhage   |  |                  |  |
|  | Additional description: Blepharitis              |                  |  |
|  | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%)  |  |
|  | 0  | 1                |  |
|  | Additional description: Blepharospasm            |                  |  |
|  | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%)  |  |
|  | 0  | 1                |  |
|  | Additional description: Blindness                |                  |  |
|  | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%)  |  |
|  | 0  | 1                |  |
|  | Additional description: Cataract                 |                  |  |
|  | 2 / 168 (1.19%)                                  | 6 / 170 (3.53%)  |  |
|  | 2  | 6                |  |
|  | Additional description: Conjunctival haemorrhage |                  |  |

|                                 |   |                 |  |
|---------------------------------|---|-----------------|--|
| subjects affected / exposed     | 2 / 168 (1.19%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 2   | 1               |  |
| Dacryostenosis acquired         | Additional description: Dacryostenosis acquired         |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 1               |  |
| Diplopia                        | Additional description: Diplopia                        |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 1               |  |
| Dry eye                         | Additional description: Dry eye                         |                 |  |
| subjects affected / exposed     | 1 / 168 (0.60%)   | 2 / 170 (1.18%) |  |
| occurrences (all)               | 1   | 2               |  |
| Eye haematoma                   | Additional description: Eye haematoma                   |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 1               |  |
| Eye inflammation                | Additional description: Eye inflammation                |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 2               |  |
| Eye pruritus                    | Additional description: Eye pruritus                    |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 1               |  |
| Glaucoma                        | Additional description: Glaucoma                        |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 1               |  |
| Macular degeneration            | Additional description: Macular degeneration            |                 |  |
| subjects affected / exposed     | 1 / 168 (0.60%)   | 0 / 170 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Macular oedema                  | Additional description: Macular oedema                  |                 |  |
| subjects affected / exposed     | 1 / 168 (0.60%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 1   | 1               |  |
| Posterior capsule opacification | Additional description: Posterior capsule opacification |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 1 / 170 (0.59%) |  |
| occurrences (all)               | 0   | 1               |  |
| Vision blurred                  | Additional description: Vision blurred                  |                 |  |
| subjects affected / exposed     | 0 / 168 (0.00%)   | 3 / 170 (1.76%) |  |
| occurrences (all)               | 0   | 3               |  |
| Visual acuity reduced           | Additional description: Visual acuity reduced           |                 |  |

|                             |  |                  |  |
|-----------------------------|--|------------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 2                |  |
| Visual impairment           | Additional description: Visual impairment    |                  |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 2 / 170 (1.18%)  |  |
| occurrences (all)           | 1  | 2                |  |
| Gastrointestinal disorders  |  |                  |  |
| Abdominal pain lower        | Additional description: Abdominal pain lower |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 2                |  |
| Abdominal pain              | Additional description: Abdominal pain       |                  |  |
| subjects affected / exposed | 11 / 168 (6.55%)                             | 6 / 170 (3.53%)  |  |
| occurrences (all)           | 12   | 8                |  |
| Abdominal distension        | Additional description: Abdominal distension |                  |  |
| subjects affected / exposed | 2 / 168 (1.19%)                              | 2 / 170 (1.18%)  |  |
| occurrences (all)           | 2  | 2                |  |
| Abdominal discomfort        | Additional description: Abdominal discomfort |                  |  |
| subjects affected / exposed | 2 / 168 (1.19%)                              | 2 / 170 (1.18%)  |  |
| occurrences (all)           | 2  | 2                |  |
| Abdominal pain upper        | Additional description: Abdominal pain upper |                  |  |
| subjects affected / exposed | 13 / 168 (7.74%)                             | 11 / 170 (6.47%) |  |
| occurrences (all)           | 14   | 12               |  |
| Angular cheilitis           | Additional description: Angular cheilitis    |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Anal inflammation           | Additional description: Anal inflammation    |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Anal fistula                | Additional description: Anal fistula         |                  |  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 0 / 170 (0.00%)  |  |
| occurrences (all)           | 2  | 0                |  |
| Aphthous ulcer              | Additional description: Aphthous ulcer       |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 2 / 170 (1.18%)  |  |
| occurrences (all)           | 0  | 3                |  |
| Ascites                     | Additional description: Ascites              |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |



|   |   |                   |
|---|---|-------------------|
| Cheilitis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Cheilitis               |                   |
|   | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%)   |
|   | 0   | 1                 |
| Chronic gastritis<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Chronic gastritis       |                   |
|   | 2 / 168 (1.19%)                                 | 0 / 170 (0.00%)   |
|   | 2   | 0                 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Constipation            |                   |
|   | 6 / 168 (3.57%)                                 | 9 / 170 (5.29%)   |
|   | 9   | 9                 |
| Dental caries<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Dental caries           |                   |
|   | 1 / 168 (0.60%)                                 | 0 / 170 (0.00%)   |
|   | 1   | 0                 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Diarrhoea               |                   |
|   | 31 / 168 (18.45%)                               | 58 / 170 (34.12%) |
|   | 48  | 101               |
| Diarrhoea haemorrhagic<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Diarrhoea haemorrhagic  |                   |
|   | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%)   |
|   | 0   | 1                 |
| Diverticulum<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Diverticulum            |                   |
|   | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%)   |
|   | 1   | 1                 |
| Diverticulum intestinal<br>subjects affected / exposed<br>occurrences (all) | Additional description: Diverticulum intestinal |                   |
|   | 1 / 168 (0.60%)                                 | 1 / 170 (0.59%)   |
|   | 1   | 1                 |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dry mouth               |                   |
|   | 6 / 168 (3.57%)                                 | 14 / 170 (8.24%)  |
|   | 7   | 15                |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dyspepsia               |                   |
|   | 6 / 168 (3.57%)                                 | 27 / 170 (15.88%) |
|   | 7   | 66                |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dysphagia               |                   |
|   | 0 / 168 (0.00%)                                 | 3 / 170 (1.76%)   |
|   | 0   | 3                 |
| Epigastric discomfort<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Epigastric discomfort   |                   |
|   | 0 / 168 (0.00%)                                 | 1 / 170 (0.59%)   |
|   | 0   | 1                 |

|                                  |  |                 |
|----------------------------------|--|-----------------|
| Eructation                       | Additional description: Eructation                       |                 |
| subjects affected / exposed      | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |
| occurrences (all)                | 0  | 1               |
| Gastric disorder                 | Additional description: Gastric disorder                 |                 |
| subjects affected / exposed      | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |
| occurrences (all)                | 0  | 1               |
| Flatulence                       | Additional description: Flatulence                       |                 |
| subjects affected / exposed      | 3 / 168 (1.79%)  | 4 / 170 (2.35%) |
| occurrences (all)                | 3  | 5               |
| Frequent bowel movements         | Additional description: Frequent bowel movements         |                 |
| subjects affected / exposed      | 2 / 168 (1.19%)  | 0 / 170 (0.00%) |
| occurrences (all)                | 2  | 0               |
| Glossodynia                      | Additional description: Glossodynia                      |                 |
| subjects affected / exposed      | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |
| occurrences (all)                | 0  | 1               |
| Gastritis                        | Additional description: Gastritis                        |                 |
| subjects affected / exposed      | 0 / 168 (0.00%)  | 7 / 170 (4.12%) |
| occurrences (all)                | 0  | 7               |
| Gastrointestinal disorder        | Additional description: Gastrointestinal disorder        |                 |
| subjects affected / exposed      | 1 / 168 (0.60%)  | 1 / 170 (0.59%) |
| occurrences (all)                | 1  | 1               |
| Gastrointestinal pain            | Additional description: Gastrointestinal pain            |                 |
| subjects affected / exposed      | 1 / 168 (0.60%)  | 2 / 170 (1.18%) |
| occurrences (all)                | 1  | 2               |
| Gastrooesophageal reflux disease | Additional description: Gastrooesophageal reflux disease |                 |
| subjects affected / exposed      | 2 / 168 (1.19%)  | 7 / 170 (4.12%) |
| occurrences (all)                | 2  | 7               |
| Gingival bleeding                | Additional description: Gingival bleeding                |                 |
| subjects affected / exposed      | 1 / 168 (0.60%)  | 2 / 170 (1.18%) |
| occurrences (all)                | 1  | 3               |
| Gingival disorder                | Additional description: Gingival disorder                |                 |
| subjects affected / exposed      | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |
| occurrences (all)                | 0  | 1               |
| Gingival swelling                | Additional description: Gingival swelling                |                 |
| subjects affected / exposed      | 0 / 168 (0.00%)  | 1 / 170 (0.59%) |
| occurrences (all)                | 0  | 1               |

|   |   |                      |
|---|---|----------------------|
| Gingivitis ulcerative<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Gingivitis ulcerative   |                      |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1 |
| Glossitis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Glossitis               |                      |
|   | 0 / 168 (0.00%)<br>0                            | 3 / 170 (1.76%)<br>7 |
| Gastric ulcer<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Gastric ulcer           |                      |
|   | 1 / 168 (0.60%)<br>1                            | 0 / 170 (0.00%)<br>0 |
| Haematochezia<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Haematochezia           |                      |
|   | 1 / 168 (0.60%)<br>1                            | 3 / 170 (1.76%)<br>3 |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Haemorrhoids            |                      |
|   | 4 / 168 (2.38%)<br>5                            | 2 / 170 (1.18%)<br>2 |
| Haemorrhoids thrombosed<br>subjects affected / exposed<br>occurrences (all) | Additional description: Haemorrhoids thrombosed |                      |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1 |
| Hiatus hernia<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Hiatus hernia           |                      |
|   | 3 / 168 (1.79%)<br>3                            | 2 / 170 (1.18%)<br>2 |
| Intestinal polyp<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Intestinal polyp        |                      |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1 |
| Large intestine polyp<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Large intestine polyp   |                      |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1 |
| Lip blister<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Lip blister             |                      |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>2 |
| Loose tooth<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Loose tooth             |                      |
|   | 1 / 168 (0.60%)<br>1                            | 0 / 170 (0.00%)<br>0 |
| Mouth swelling<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Mouth swelling          |                      |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1 |

|   |   |                         |
|---|---|-------------------------|
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Mouth ulceration        |                         |
|   | 0 / 168 (0.00%)<br>0                            | 2 / 170 (1.18%)<br>4    |
| Melaena<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Melaena                 |                         |
|   | 2 / 168 (1.19%)<br>2                            | 1 / 170 (0.59%)<br>1    |
| Mouth haemorrhage<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Mouth haemorrhage       |                         |
|   | 0 / 168 (0.00%)<br>0                            | 2 / 170 (1.18%)<br>3    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Nausea                  |                         |
|   | 20 / 168 (11.90%)<br>30                         | 32 / 170 (18.82%)<br>57 |
| Noninfective gingivitis<br>subjects affected / exposed<br>occurrences (all) | Additional description: Noninfective gingivitis |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |
| Obstruction gastric<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Obstruction gastric     |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>2    |
| Oesophageal pain<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Oesophageal pain        |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |
| Oesophagitis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Oesophagitis            |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |
| Oral disorder<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Oral disorder           |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |
| Oral pain<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Oral pain               |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |
| Pancreatic cyst<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Pancreatic cyst         |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |
| Paraesthesia oral<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Paraesthesia oral       |                         |
|   | 0 / 168 (0.00%)<br>0                            | 1 / 170 (0.59%)<br>1    |

|  |  |                        |
|--|--|------------------------|
| Proctitis<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Proctitis                  |                        |
|  | 0 / 168 (0.00%)<br>0                               | 1 / 170 (0.59%)<br>2   |
| Rectal prolapse<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Rectal prolapse            |                        |
|  | 0 / 168 (0.00%)<br>0                               | 1 / 170 (0.59%)<br>1   |
| Salivary gland enlargement<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Salivary gland enlargement |                        |
|  | 1 / 168 (0.60%)<br>1                               | 0 / 170 (0.00%)<br>0   |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Stomatitis                 |                        |
|  | 2 / 168 (1.19%)<br>2                               | 13 / 170 (7.65%)<br>20 |
| Subileus<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Subileus                   |                        |
|  | 1 / 168 (0.60%)<br>1                               | 0 / 170 (0.00%)<br>0   |
| Tongue blistering<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Tongue blistering          |                        |
|  | 0 / 168 (0.00%)<br>0                               | 1 / 170 (0.59%)<br>1   |
| Tongue ulceration<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Tongue ulceration          |                        |
|  | 1 / 168 (0.60%)<br>1                               | 1 / 170 (0.59%)<br>1   |
| Toothache<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Toothache                  |                        |
|  | 3 / 168 (1.79%)<br>3                               | 3 / 170 (1.76%)<br>4   |
| Umbilical hernia<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Umbilical hernia           |                        |
|  | 1 / 168 (0.60%)<br>1                               | 0 / 170 (0.00%)<br>0   |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Vomiting                   |                        |
|  | 7 / 168 (4.17%)<br>9                               | 13 / 170 (7.65%)<br>16 |
| Hepatobiliary disorders<br>Cholecystitis acute<br>subjects affected / exposed<br>occurrences (all)<br><br>Cholelithiasis |  |                        |
|  | Additional description: Cholecystitis acute        |                        |
|  | 0 / 168 (0.00%)<br>0                               | 1 / 170 (0.59%)<br>1   |
|  | Additional description: Cholelithiasis             |                        |

|  |   |                 |  |
|--|---|-----------------|--|
| subjects affected / exposed            | 1 / 168 (0.60%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 1   | 1               |  |
| Hepatic cyst                           | Additional description: Hepatic cyst        |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0   | 1               |  |
| Hepatic steatosis                      | Additional description: Hepatic steatosis   |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 2 / 170 (1.18%) |  |
| occurrences (all)                      | 0   | 2               |  |
| Hyperbilirubinaemia                    | Additional description: Hyperbilirubinaemia |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0   | 1               |  |
| Skin and subcutaneous tissue disorders |   |                 |  |
| Actinic keratosis                      | Additional description: Actinic keratosis   |                 |  |
| subjects affected / exposed            | 4 / 168 (2.38%)                             | 2 / 170 (1.18%) |  |
| occurrences (all)                      | 4   | 4               |  |
| Alopecia areata                        | Additional description: Alopecia areata     |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0   | 1               |  |
| Alopecia                               | Additional description: Alopecia            |                 |  |
| subjects affected / exposed            | 4 / 168 (2.38%)                             | 5 / 170 (2.94%) |  |
| occurrences (all)                      | 4   | 5               |  |
| Asteatosis                             | Additional description: Asteatosis          |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0   | 1               |  |
| Blood blister                          | Additional description: Blood blister       |                 |  |
| subjects affected / exposed            | 1 / 168 (0.60%)                             | 0 / 170 (0.00%) |  |
| occurrences (all)                      | 1   | 0               |  |
| Butterfly rash                         | Additional description: Butterfly rash      |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0   | 1               |  |
| Dandruff                               | Additional description: Dandruff            |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)                      | 0   | 1               |  |
| Dermatitis                             | Additional description: Dermatitis          |                 |  |
| subjects affected / exposed            | 0 / 168 (0.00%)                             | 2 / 170 (1.18%) |  |
| occurrences (all)                      | 0   | 3               |  |

|  |  |                        |
|--|--|------------------------|
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Dermatitis acneiform     |                        |
|  | 0 / 168 (0.00%)<br>0                             | 3 / 170 (1.76%)<br>5   |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Dermatitis allergic      |                        |
|  | 1 / 168 (0.60%)<br>1                             | 2 / 170 (1.18%)<br>2   |
| Dermatitis atopic<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Dermatitis atopic        |                        |
|  | 1 / 168 (0.60%)<br>1                             | 1 / 170 (0.59%)<br>1   |
| Dermatitis bullous<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Dermatitis bullous       |                        |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0   |
| Dermatosis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dermatitis               |                        |
|  | 1 / 168 (0.60%)<br>1                             | 1 / 170 (0.59%)<br>1   |
| Dermal cyst<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Dermal cyst              |                        |
|  | 1 / 168 (0.60%)<br>1                             | 3 / 170 (1.76%)<br>3   |
| Ecchymosis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Ecchymosis               |                        |
|  | 1 / 168 (0.60%)<br>1                             | 2 / 170 (1.18%)<br>3   |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Eczema                   |                        |
|  | 1 / 168 (0.60%)<br>1                             | 7 / 170 (4.12%)<br>9   |
| Drug eruption<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Drug eruption            |                        |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1   |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Dry skin                 |                        |
|  | 5 / 168 (2.98%)<br>5                             | 16 / 170 (9.41%)<br>19 |
| Erythema<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Erythema                 |                        |
|  | 1 / 168 (0.60%)<br>1                             | 3 / 170 (1.76%)<br>3   |
| Haemorrhage subcutaneous<br>subjects affected / exposed<br>occurrences (all) | Additional description: Haemorrhage subcutaneous |                        |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1   |

|   |   |                         |
|---|---|-------------------------|
| Hair colour changes<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Hair colour changes   |                         |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1    |
| Hair growth abnormal<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Hair growth abnormal  |                         |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1    |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Hyperhidrosis         |                         |
|   | 7 / 168 (4.17%)<br>10                         | 4 / 170 (2.35%)<br>4    |
| Hyperkeratosis<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Hyperkeratosis        |                         |
|   | 1 / 168 (0.60%)<br>1                          | 0 / 170 (0.00%)<br>0    |
| Ingrowing nail<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Ingrowing nail        |                         |
|   | 0 / 168 (0.00%)<br>0                          | 5 / 170 (2.94%)<br>5    |
| Nail atrophy<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Nail atrophy          |                         |
|   | 1 / 168 (0.60%)<br>1                          | 0 / 170 (0.00%)<br>0    |
| Nail bed inflammation<br>subjects affected / exposed<br>occurrences (all) | Additional description: Nail bed inflammation |                         |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1    |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Nail disorder         |                         |
|   | 0 / 168 (0.00%)<br>0                          | 2 / 170 (1.18%)<br>2    |
| Nail dystrophy<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Nail dystrophy        |                         |
|   | 0 / 168 (0.00%)<br>0                          | 1 / 170 (0.59%)<br>1    |
| Nail ridging<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Nail ridging          |                         |
|   | 0 / 168 (0.00%)<br>0                          | 4 / 170 (2.35%)<br>4    |
| Night sweats<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Night sweats          |                         |
|   | 9 / 168 (5.36%)<br>14                         | 5 / 170 (2.94%)<br>7    |
| Onychoclasia<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Onychoclasia          |                         |
|   | 3 / 168 (1.79%)<br>3                          | 19 / 170 (11.18%)<br>19 |



|                             |  |                   |
|-----------------------------|--|-------------------|
| Onycholysis                 | Additional description: Onycholysis                |                   |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)   |
| occurrences (all)           | 0  | 1                 |
| Pain of skin                | Additional description: Pain of skin               |                   |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)   |
| occurrences (all)           | 0  | 1                 |
| Petechiae                   | Additional description: Petechiae                  |                   |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 7 / 170 (4.12%)   |
| occurrences (all)           | 0  | 9                 |
| Photosensitivity reaction   | Additional description: Photosensitivity reaction  |                   |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%)   |
| occurrences (all)           | 1  | 0                 |
| Polymorphic light eruption  | Additional description: Polymorphic light eruption |                   |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)   |
| occurrences (all)           | 0  | 1                 |
| Pruritus                    | Additional description: Pruritus                   |                   |
| subjects affected / exposed | 6 / 168 (3.57%)                                    | 13 / 170 (7.65%)  |
| occurrences (all)           | 7  | 15                |
| Psoriasis                   | Additional description: Psoriasis                  |                   |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%)   |
| occurrences (all)           | 1  | 0                 |
| Purpura                     | Additional description: Purpura                    |                   |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 2 / 170 (1.18%)   |
| occurrences (all)           | 0  | 2                 |
| Rash                        | Additional description: Rash                       |                   |
| subjects affected / exposed | 10 / 168 (5.95%)                                   | 33 / 170 (19.41%) |
| occurrences (all)           | 15   | 44                |
| Rash erythematous           | Additional description: Rash erythematous          |                   |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)   |
| occurrences (all)           | 0  | 1                 |
| Rash maculo-papular         | Additional description: Rash maculo-papular        |                   |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 2 / 170 (1.18%)   |
| occurrences (all)           | 1  | 9                 |
| Rash papular                | Additional description: Rash papular               |                   |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%)   |
| occurrences (all)           | 1  | 0                 |

|                             |  |                 |
|-----------------------------|--|-----------------|
| Scalp disorder              | Additional description: Scalp disorder         |                 |
| subjects affected / exposed | 1 / 168 (0.60%)                                | 0 / 170 (0.00%) |
| occurrences (all)           | 1  | 0               |
| Seborrhoeic dermatitis      | Additional description: Seborrhoeic dermatitis |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |
| occurrences (all)           | 0  | 1               |
| Skin discolouration         | Additional description: Skin discolouration    |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |
| occurrences (all)           | 0  | 1               |
| Skin disorder               | Additional description: Skin disorder          |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |
| occurrences (all)           | 0  | 1               |
| Skin erosion                | Additional description: Skin erosion           |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |
| occurrences (all)           | 0  | 1               |
| Skin fissures               | Additional description: Skin fissures          |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 8 / 170 (4.71%) |
| occurrences (all)           | 0  | 10              |
| Skin haemorrhage            | Additional description: Skin haemorrhage       |                 |
| subjects affected / exposed | 1 / 168 (0.60%)                                | 2 / 170 (1.18%) |
| occurrences (all)           | 1  | 2               |
| Skin hyperpigmentation      | Additional description: Skin hyperpigmentation |                 |
| subjects affected / exposed | 1 / 168 (0.60%)                                | 0 / 170 (0.00%) |
| occurrences (all)           | 1  | 0               |
| Skin induration             | Additional description: Skin induration        |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |
| occurrences (all)           | 0  | 1               |
| Skin irritation             | Additional description: Skin irritation        |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 2 / 170 (1.18%) |
| occurrences (all)           | 0  | 2               |
| Skin lesion                 | Additional description: Skin lesion            |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 3 / 170 (1.76%) |
| occurrences (all)           | 0  | 3               |
| Skin sensitisation          | Additional description: Skin sensitisation     |                 |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |
| occurrences (all)           | 0  | 1               |

|   |   |                 |
|---|---|-----------------|
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Skin ulcer            |                 |
|   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%) |
|   | 1   | 0               |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Swelling face         |                 |
|   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%) |
|   | 1   | 0               |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Urticaria             |                 |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |
|   | 0   | 1               |
| Renal and urinary disorders   |   |                 |
| Chromaturia<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Chromaturia           |                 |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |
|   | 0   | 1               |
| Cystitis noninfective<br>subjects affected / exposed<br>occurrences (all) | Additional description: Cystitis noninfective |                 |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |
|   | 0   | 1               |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dysuria               |                 |
|   | 2 / 168 (1.19%)                               | 2 / 170 (1.18%) |
|   | 2   | 3               |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Haematuria            |                 |
|   | 3 / 168 (1.79%)                               | 6 / 170 (3.53%) |
|   | 4   | 9               |
| Incontinence<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Incontinence          |                 |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |
|   | 0   | 1               |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Micturition urgency   |                 |
|   | 1 / 168 (0.60%)                               | 1 / 170 (0.59%) |
|   | 1   | 1               |
| Nocturia<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Nocturia              |                 |
|   | 3 / 168 (1.79%)                               | 1 / 170 (0.59%) |
|   | 3   | 1               |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Pollakiuria           |                 |
|   | 6 / 168 (3.57%)                               | 0 / 170 (0.00%) |
|   | 6   | 0               |
| Renal cyst  | Additional description: Renal cyst            |                 |
|   |   |                 |
|   |   |                 |

|                               |   |                 |  |
|-------------------------------|---|-----------------|--|
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 2 / 170 (1.18%) |  |
| occurrences (all)             | 0   | 2               |  |
| Renal failure                 | Additional description: Renal failure                 |                 |  |
| subjects affected / exposed   | 2 / 168 (1.19%)                                       | 3 / 170 (1.76%) |  |
| occurrences (all)             | 2   | 3               |  |
| Renal pain                    | Additional description: Renal pain                    |                 |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 2 / 170 (1.18%) |  |
| occurrences (all)             | 0   | 2               |  |
| Urinary incontinence          | Additional description: Urinary incontinence          |                 |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 1 / 170 (0.59%) |  |
| occurrences (all)             | 1   | 1               |  |
| Endocrine disorders           |   |                 |  |
| Goitre                        | Additional description: Goitre                        |                 |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%) |  |
| occurrences (all)             | 1   | 0               |  |
| Hashimoto's disease           | Additional description: Hashimoto's disease           |                 |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%) |  |
| occurrences (all)             | 1   | 0               |  |
| Hyperparathyroidism           | Additional description: Hyperparathyroidism           |                 |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences (all)             | 0   | 1               |  |
| Hyperparathyroidism secondary | Additional description: Hyperparathyroidism secondary |                 |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences (all)             | 0   | 1               |  |
| Hypogonadism                  | Additional description: Hypogonadism                  |                 |  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%) |  |
| occurrences (all)             | 1   | 0               |  |
| Hypothyroidism                | Additional description: Hypothyroidism                |                 |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences (all)             | 0   | 1               |  |
| Thyroid calcification         | Additional description: Thyroid calcification         |                 |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences (all)             | 0   | 1               |  |
| Thyroid mass                  | Additional description: Thyroid mass                  |                 |  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%) |  |
| occurrences (all)             | 0   | 1               |  |

|  |  |                         |
|--|--|-------------------------|
| Type 2 diabetes mellitus<br>subjects affected / exposed<br>occurrences (all) | Additional description: Type 2 diabetes mellitus |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Musculoskeletal and connective tissue disorders                              | Additional description: Arthralgia               |                         |
|  | 15 / 168 (8.93%)<br>18                           | 30 / 170 (17.65%)<br>37 |
|  | Additional description: Arthritis                |                         |
|  | 1 / 168 (0.60%)<br>1                             | 2 / 170 (1.18%)<br>2    |
|  | Additional description: Arthritis reactive       |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
|  | Additional description: Arthropathy              |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
|  | Additional description: Back pain                |                         |
|  | 20 / 168 (11.90%)<br>24                          | 20 / 170 (11.76%)<br>24 |
|  | Additional description: Barrel chest             |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
|  | Additional description: Bone pain                |                         |
|  | 2 / 168 (1.19%)<br>2                             | 2 / 170 (1.18%)<br>2    |
|  | Additional description: Bursitis                 |                         |
|  | 2 / 168 (1.19%)<br>2                             | 2 / 170 (1.18%)<br>2    |
|  | Additional description: Collagen disorder        |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1    |
|  | Additional description: Exostosis                |                         |
|  | 1 / 168 (0.60%)<br>1                             | 2 / 170 (1.18%)<br>2    |
|  | Additional description: Flank pain               |                         |

|                                |  |                   |  |
|--------------------------------|--|-------------------|--|
| subjects affected / exposed    | 2 / 168 (1.19%)  | 2 / 170 (1.18%)   |  |
| occurrences (all)              | 2  | 2                 |  |
| Foot deformity                 | Additional description: Foot deformity                 |                   |  |
| subjects affected / exposed    | 3 / 168 (1.79%)  | 1 / 170 (0.59%)   |  |
| occurrences (all)              | 3  | 1                 |  |
| Groin pain                     | Additional description: Groin pain                     |                   |  |
| subjects affected / exposed    | 1 / 168 (0.60%)  | 0 / 170 (0.00%)   |  |
| occurrences (all)              | 1  | 0                 |  |
| Hypercreatinaemia              | Additional description: Hypercreatinaemia              |                   |  |
| subjects affected / exposed    | 2 / 168 (1.19%)  | 1 / 170 (0.59%)   |  |
| occurrences (all)              | 2  | 1                 |  |
| Joint effusion                 | Additional description: Joint effusion                 |                   |  |
| subjects affected / exposed    | 0 / 168 (0.00%)  | 1 / 170 (0.59%)   |  |
| occurrences (all)              | 0  | 1                 |  |
| Joint swelling                 | Additional description: Joint swelling                 |                   |  |
| subjects affected / exposed    | 0 / 168 (0.00%)  | 2 / 170 (1.18%)   |  |
| occurrences (all)              | 0  | 2                 |  |
| Intervertebral disc disorder   | Additional description: Intervertebral disc disorder   |                   |  |
| subjects affected / exposed    | 1 / 168 (0.60%)  | 0 / 170 (0.00%)   |  |
| occurrences (all)              | 1  | 0                 |  |
| Intervertebral disc protrusion | Additional description: Intervertebral disc protrusion |                   |  |
| subjects affected / exposed    | 2 / 168 (1.19%)  | 3 / 170 (1.76%)   |  |
| occurrences (all)              | 2  | 3                 |  |
| Jaw cyst                       | Additional description: Jaw cyst                       |                   |  |
| subjects affected / exposed    | 1 / 168 (0.60%)  | 0 / 170 (0.00%)   |  |
| occurrences (all)              | 1  | 0                 |  |
| Limb discomfort                | Additional description: Limb discomfort                |                   |  |
| subjects affected / exposed    | 1 / 168 (0.60%)  | 0 / 170 (0.00%)   |  |
| occurrences (all)              | 1  | 0                 |  |
| Muscle atrophy                 | Additional description: Muscle atrophy                 |                   |  |
| subjects affected / exposed    | 1 / 168 (0.60%)  | 0 / 170 (0.00%)   |  |
| occurrences (all)              | 1  | 0                 |  |
| Muscle spasms                  | Additional description: Muscle spasms                  |                   |  |
| subjects affected / exposed    | 6 / 168 (3.57%)  | 25 / 170 (14.71%) |  |
| occurrences (all)              | 9  | 52                |  |
| Muscle twitching               | Additional description: Muscle twitching               |                   |  |

|                             |  |                  |  |
|-----------------------------|--|------------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 2 / 170 (1.18%)  |  |
| occurrences (all)           | 0  | 2                |  |
| Muscular weakness           | Additional description: Muscular weakness          |                  |  |
| subjects affected / exposed | 2 / 168 (1.19%)                                    | 3 / 170 (1.76%)  |  |
| occurrences (all)           | 3  | 3                |  |
| Musculoskeletal chest pain  | Additional description: Musculoskeletal chest pain |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Musculoskeletal disorder    | Additional description: Musculoskeletal disorder   |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Musculoskeletal pain        | Additional description: Musculoskeletal pain       |                  |  |
| subjects affected / exposed | 5 / 168 (2.98%)                                    | 4 / 170 (2.35%)  |  |
| occurrences (all)           | 6  | 5                |  |
| Musculoskeletal stiffness   | Additional description: Musculoskeletal stiffness  |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 2                |  |
| Myalgia                     | Additional description: Myalgia                    |                  |  |
| subjects affected / exposed | 8 / 168 (4.76%)                                    | 12 / 170 (7.06%) |  |
| occurrences (all)           | 9  | 12               |  |
| Myositis                    | Additional description: Myositis                   |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Neck pain                   | Additional description: Neck pain                  |                  |  |
| subjects affected / exposed | 4 / 168 (2.38%)                                    | 2 / 170 (1.18%)  |  |
| occurrences (all)           | 4  | 2                |  |
| Muscle tightness            | Additional description: Muscle tightness           |                  |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                    | 3 / 170 (1.76%)  |  |
| occurrences (all)           | 1  | 3                |  |
| Osteoporosis                | Additional description: Osteoporosis               |                  |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Pain in extremity           | Additional description: Pain in extremity          |                  |  |
| subjects affected / exposed | 15 / 168 (8.93%)                                   | 15 / 170 (8.82%) |  |
| occurrences (all)           | 17   | 21               |  |
| Pain in jaw                 | Additional description: Pain in jaw                |                  |  |

|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 1 / 168 (0.60%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Osteoarthritis              | Additional description: Osteoarthritis        |                 |  |
| subjects affected / exposed | 11 / 168 (6.55%)                              | 3 / 170 (1.76%) |  |
| occurrences (all)           | 11  | 4               |  |
| Periarthritis               | Additional description: Periarthritis         |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Periostitis                 | Additional description: Periostitis           |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Plantar fasciitis           | Additional description: Plantar fasciitis     |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Plica syndrome              | Additional description: Plica syndrome        |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Rheumatic disorder          | Additional description: Rheumatic disorder    |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Spinal osteoarthritis       | Additional description: Spinal osteoarthritis |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Spinal pain                 | Additional description: Spinal pain           |                 |  |
| subjects affected / exposed | 2 / 168 (1.19%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 2   | 0               |  |
| Spinal stenosis             | Additional description: Spinal stenosis       |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                               | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Synovial cyst               | Additional description: Synovial cyst         |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 2               |  |
| Tendon discomfort           | Additional description: Tendon discomfort     |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                               | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Tendonitis                  | Additional description: Tendonitis            |                 |  |



|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 1 / 168 (0.60%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Tenosynovitis               | Additional description: Tenosynovitis       |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Torticollis                 | Additional description: Torticollis         |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Infections and infestations |   |                 |  |
| Acne pustular               | Additional description: Acne pustular       |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Abscess limb                | Additional description: Abscess limb        |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0   | 3               |  |
| Abscess                     | Additional description: Abscess             |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1   | 1               |  |
| Angular cheilitis           | Additional description: Angular cheilitis   |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 2               |  |
| Alveolar osteitis           | Additional description: Alveolar osteitis   |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                             | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Bacterial diarrhoea         | Additional description: Bacterial diarrhoea |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                             | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Arthritis infective         | Additional description: Arthritis infective |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                             | 0 / 170 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Atypical pneumonia          | Additional description: Atypical pneumonia  |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |
| Bacterial rhinitis          | Additional description: Bacterial rhinitis  |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                             | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0   | 1               |  |

|  |  |                         |
|--|--|-------------------------|
| Bacterial vaginosis<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Bacterial vaginosis      |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Bacterial food poisoning<br>subjects affected / exposed<br>occurrences (all) | Additional description: Bacterial food poisoning |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Bacterial infection<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Bacterial infection      |                         |
|  | 1 / 168 (0.60%)<br>1                             | 1 / 170 (0.59%)<br>1    |
| Bacterial pyelonephritis<br>subjects affected / exposed<br>occurrences (all) | Additional description: Bacterial pyelonephritis |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Bronchitis               |                         |
|  | 19 / 168 (11.31%)<br>21                          | 26 / 170 (15.29%)<br>30 |
| Bronchitis bacterial<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Bronchitis bacterial     |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>1    |
| Bronchitis viral<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Bronchitis viral         |                         |
|  | 0 / 168 (0.00%)<br>0                             | 2 / 170 (1.18%)<br>2    |
| Bursitis infective<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Bursitis infective       |                         |
|  | 1 / 168 (0.60%)<br>1                             | 1 / 170 (0.59%)<br>1    |
| Campylobacter infection<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Campylobacter infection  |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Candida infection<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Candida infection        |                         |
|  | 0 / 168 (0.00%)<br>0                             | 1 / 170 (0.59%)<br>2    |
| Chronic tonsillitis<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Chronic tonsillitis      |                         |
|  | 1 / 168 (0.60%)<br>1                             | 0 / 170 (0.00%)<br>0    |
| Chronic sinusitis<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Chronic sinusitis        |                         |
|  | 1 / 168 (0.60%)<br>1                             | 2 / 170 (1.18%)<br>2    |

|                             |  |                  |
|-----------------------------|--|------------------|
| Cellulitis                  | Additional description: Cellulitis           |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |
| occurrences (all)           | 0  | 1                |
| Conjunctivitis              | Additional description: Conjunctivitis       |                  |
| subjects affected / exposed | 3 / 168 (1.79%)                              | 6 / 170 (3.53%)  |
| occurrences (all)           | 3  | 9                |
| COVID-19                    | Additional description: COVID-19             |                  |
| subjects affected / exposed | 7 / 168 (4.17%)                              | 7 / 170 (4.12%)  |
| occurrences (all)           | 7  | 7                |
| Cystitis                    | Additional description: Cystitis             |                  |
| subjects affected / exposed | 12 / 168 (7.14%)                             | 10 / 170 (5.88%) |
| occurrences (all)           | 20   | 21               |
| Cystitis bacterial          | Additional description: Cystitis bacterial   |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 1 / 170 (0.59%)  |
| occurrences (all)           | 0  | 1                |
| Dermatitis infected         | Additional description: Dermatitis infected  |                  |
| subjects affected / exposed | 3 / 168 (1.79%)                              | 0 / 170 (0.00%)  |
| occurrences (all)           | 3  | 0                |
| Diarrhoea infectious        | Additional description: Diarrhoea infectious |                  |
| subjects affected / exposed | 2 / 168 (1.19%)                              | 3 / 170 (1.76%)  |
| occurrences (all)           | 2  | 3                |
| Diverticulitis              | Additional description: Diverticulitis       |                  |
| subjects affected / exposed | 2 / 168 (1.19%)                              | 1 / 170 (0.59%)  |
| occurrences (all)           | 4  | 1                |
| Ear infection               | Additional description: Ear infection        |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 1 / 170 (0.59%)  |
| occurrences (all)           | 1  | 1                |
| Epididymitis                | Additional description: Epididymitis         |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 2 / 170 (1.18%)  |
| occurrences (all)           | 0  | 6                |
| Erysipelas                  | Additional description: Erysipelas           |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                              | 2 / 170 (1.18%)  |
| occurrences (all)           | 1  | 2                |
| Eye infection               | Additional description: Eye infection        |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                              | 2 / 170 (1.18%)  |
| occurrences (all)           | 0  | 2                |

|  |  |                 |
|--|--|-----------------|
| Eyelid infection<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Eyelid infection             |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |
| Enterococcal infection<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Enterococcal infection       |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |
| Febrile infection<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Febrile infection            |                 |
|  | 3 / 168 (1.79%)                                      | 1 / 170 (0.59%) |
|  | 3  | 1               |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Folliculitis                 |                 |
|  | 2 / 168 (1.19%)                                      | 3 / 170 (1.76%) |
|  | 2  | 3               |
| Fungal infection<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Fungal infection             |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |
| Fungal pharyngitis<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Fungal pharyngitis           |                 |
|  | 1 / 168 (0.60%)                                      | 0 / 170 (0.00%) |
|  | 1  | 0               |
| Fungal skin infection<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Fungal skin infection        |                 |
|  | 1 / 168 (0.60%)                                      | 1 / 170 (0.59%) |
|  | 1  | 1               |
| Gastric infection<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Gastric infection            |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Gastroenteritis              |                 |
|  | 5 / 168 (2.98%)                                      | 5 / 170 (2.94%) |
|  | 6  | 7               |
| Gastroenteritis norovirus<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Gastroenteritis norovirus    |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |
| Gastroenteritis viral<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Gastroenteritis viral        |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |
| Gastrointestinal candidiasis<br>subjects affected / exposed<br>occurrences (all) | Additional description: Gastrointestinal candidiasis |                 |
|  | 0 / 168 (0.00%)                                      | 1 / 170 (0.59%) |
|  | 0  | 1               |

|  |  |                  |
|--|--|------------------|
| Gastrointestinal infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Gastrointestinal infection |                  |
|  | 13 / 168 (7.74%)                                   | 15 / 170 (8.82%) |
|  | 14   | 26               |
| Genital herpes<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Genital herpes             |                  |
|  | 1 / 168 (0.60%)                                    | 0 / 170 (0.00%)  |
|  | 1  | 0                |
| Genital herpes zoster<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Genital herpes zoster      |                  |
|  | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |
|  | 0  | 1                |
| Gingivitis<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Gingivitis                 |                  |
|  | 2 / 168 (1.19%)                                    | 2 / 170 (1.18%)  |
|  | 2  | 2                |
| Haemophilus infection<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Haemophilus infection      |                  |
|  | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |
|  | 0  | 1                |
| Helicobacter gastritis<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Helicobacter gastritis     |                  |
|  | 2 / 168 (1.19%)                                    | 2 / 170 (1.18%)  |
|  | 2  | 2                |
| Hepatitis E<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Hepatitis E                |                  |
|  | 1 / 168 (0.60%)                                    | 1 / 170 (0.59%)  |
|  | 1  | 1                |
| Herpes simplex<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Herpes simplex             |                  |
|  | 2 / 168 (1.19%)                                    | 0 / 170 (0.00%)  |
|  | 3  | 0                |
| Herpes virus infection<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Herpes virus infection     |                  |
|  | 1 / 168 (0.60%)                                    | 2 / 170 (1.18%)  |
|  | 1  | 2                |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Herpes zoster              |                  |
|  | 10 / 168 (5.95%)                                   | 5 / 170 (2.94%)  |
|  | 13   | 5                |
| Hepatitis viral<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Hepatitis viral            |                  |
|  | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |
|  | 0  | 1                |
| Impetigo<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Impetigo                   |                  |
|  | 0 / 168 (0.00%)                                    | 1 / 170 (0.59%)  |
|  | 0  | 1                |

|   |   |                        |
|---|---|------------------------|
| Infected bite<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Infected bite                     |                        |
|   | 3 / 168 (1.79%)<br>3                                      | 0 / 170 (0.00%)<br>0   |
| Infected bites<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Infected bites                    |                        |
|   | 1 / 168 (0.60%)<br>1                                      | 0 / 170 (0.00%)<br>0   |
| Infected cyst<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Infected cyst                     |                        |
|   | 1 / 168 (0.60%)<br>1                                      | 0 / 170 (0.00%)<br>0   |
| Infection<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Infection                         |                        |
|   | 12 / 168 (7.14%)<br>13                                    | 9 / 170 (5.29%)<br>14  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Influenza                         |                        |
|   | 8 / 168 (4.76%)<br>13                                     | 12 / 170 (7.06%)<br>22 |
| Injection site abscess<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Injection site abscess            |                        |
|   | 0 / 168 (0.00%)<br>0                                      | 1 / 170 (0.59%)<br>1   |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)                        | Additional description: Laryngitis                        |                        |
|   | 0 / 168 (0.00%)<br>0                                      | 4 / 170 (2.35%)<br>4   |
| Lip infection<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Lip infection                     |                        |
|   | 0 / 168 (0.00%)<br>0                                      | 2 / 170 (1.18%)<br>4   |
| Localised infection<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Localised infection               |                        |
|   | 0 / 168 (0.00%)<br>0                                      | 2 / 170 (1.18%)<br>2   |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Lower respiratory tract infection |                        |
|   | 1 / 168 (0.60%)<br>1                                      | 1 / 170 (0.59%)<br>1   |
| Lyme disease<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Lyme disease                      |                        |
|   | 0 / 168 (0.00%)<br>0                                      | 1 / 170 (0.59%)<br>1   |
| Mucosal infection<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Mucosal infection                 |                        |
|   | 0 / 168 (0.00%)<br>0                                      | 1 / 170 (0.59%)<br>2   |

|   |   |                   |
|---|---|-------------------|
| Nail bed infection<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Nail bed infection    |                   |
|   | 1 / 168 (0.60%)                               | 2 / 170 (1.18%)   |
|   | 1   | 2                 |
| Nail infection<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Nail infection        |                   |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)   |
|   | 0   | 1                 |
| Nasal herpes<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Nasal herpes          |                   |
|   | 1 / 168 (0.60%)                               | 0 / 170 (0.00%)   |
|   | 1   | 0                 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Nasopharyngitis       |                   |
|   | 72 / 168 (42.86%)                             | 51 / 170 (30.00%) |
|   | 126   | 108               |
| Neutropenic infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Neutropenic infection |                   |
|   | 2 / 168 (1.19%)                               | 0 / 170 (0.00%)   |
|   | 2   | 0                 |
| Nosocomial infection<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Nosocomial infection  |                   |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)   |
|   | 0   | 1                 |
| Onychomycosis<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Onychomycosis         |                   |
|   | 1 / 168 (0.60%)                               | 1 / 170 (0.59%)   |
|   | 1   | 1                 |
| Oral fungal infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Oral fungal infection |                   |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)   |
|   | 0   | 1                 |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Oral herpes           |                   |
|   | 12 / 168 (7.14%)                              | 2 / 170 (1.18%)   |
|   | 18  | 6                 |
| Oral infection<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Oral infection        |                   |
|   | 0 / 168 (0.00%)                               | 3 / 170 (1.76%)   |
|   | 0   | 3                 |
| Oral viral infection<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Oral viral infection  |                   |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)   |
|   | 0   | 1                 |
| Orchitis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Orchitis              |                   |
|   | 0 / 168 (0.00%)                               | 1 / 170 (0.59%)   |
|   | 0   | 1                 |

|                               |   |                  |
|-------------------------------|---|------------------|
| Otitis externa                | Additional description: Otitis externa                |                  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%)  |
| occurrences (all)             | 1   | 0                |
| Paronychia                    | Additional description: Paronychia                    |                  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 10 / 170 (5.88%) |
| occurrences (all)             | 3   | 12               |
| Parotitis                     | Additional description: Parotitis                     |                  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 1 / 170 (0.59%)  |
| occurrences (all)             | 3   | 1                |
| Penile infection              | Additional description: Penile infection              |                  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)  |
| occurrences (all)             | 0   | 1                |
| Periodontitis                 | Additional description: Periodontitis                 |                  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%)  |
| occurrences (all)             | 1   | 0                |
| Pharyngitis                   | Additional description: Pharyngitis                   |                  |
| subjects affected / exposed   | 4 / 168 (2.38%)                                       | 4 / 170 (2.35%)  |
| occurrences (all)             | 4   | 4                |
| Phlebitis infective           | Additional description: Phlebitis infective           |                  |
| subjects affected / exposed   | 1 / 168 (0.60%)                                       | 0 / 170 (0.00%)  |
| occurrences (all)             | 1   | 0                |
| Pneumonia                     | Additional description: Pneumonia                     |                  |
| subjects affected / exposed   | 7 / 168 (4.17%)                                       | 10 / 170 (5.88%) |
| occurrences (all)             | 9   | 15               |
| Postoperative wound infection | Additional description: Postoperative wound infection |                  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)  |
| occurrences (all)             | 0   | 1                |
| Pseudomonas infection         | Additional description: Pseudomonas infection         |                  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)  |
| occurrences (all)             | 0   | 1                |
| Purulence                     | Additional description: Purulence                     |                  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)  |
| occurrences (all)             | 0   | 1                |
| Pyelonephritis                | Additional description: Pyelonephritis                |                  |
| subjects affected / exposed   | 0 / 168 (0.00%)                                       | 1 / 170 (0.59%)  |
| occurrences (all)             | 0   | 1                |



|                             |   |                  |
|-----------------------------|---|------------------|
| Pyoderma                    | Additional description: Pyoderma                    |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%)  |
| occurrences (all)           | 0   | 1                |
| Rash pustular               | Additional description: Rash pustular               |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                                     | 2 / 170 (1.18%)  |
| occurrences (all)           | 0   | 3                |
| Respiratory tract infection | Additional description: Respiratory tract infection |                  |
| subjects affected / exposed | 8 / 168 (4.76%)                                     | 13 / 170 (7.65%) |
| occurrences (all)           | 9   | 23               |
| Retinitis                   | Additional description: Retinitis                   |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                                     | 0 / 170 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Rhinitis                    | Additional description: Rhinitis                    |                  |
| subjects affected / exposed | 3 / 168 (1.79%)                                     | 10 / 170 (5.88%) |
| occurrences (all)           | 5   | 10               |
| Root canal infection        | Additional description: Root canal infection        |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                                     | 2 / 170 (1.18%)  |
| occurrences (all)           | 1   | 2                |
| Scarlet fever               | Additional description: Scarlet fever               |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                                     | 0 / 170 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Scrotal infection           | Additional description: Scrotal infection           |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                                     | 2 / 170 (1.18%)  |
| occurrences (all)           | 0   | 5                |
| Seminal vesicular infection | Additional description: Seminal vesicular infection |                  |
| subjects affected / exposed | 0 / 168 (0.00%)                                     | 1 / 170 (0.59%)  |
| occurrences (all)           | 0   | 1                |
| Sialoadenitis               | Additional description: Sialoadenitis               |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                                     | 0 / 170 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Sinobronchitis              | Additional description: Sinobronchitis              |                  |
| subjects affected / exposed | 1 / 168 (0.60%)                                     | 0 / 170 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Sinusitis                   | Additional description: Sinusitis                   |                  |
| subjects affected / exposed | 8 / 168 (4.76%)                                     | 9 / 170 (5.29%)  |
| occurrences (all)           | 11  | 15               |

|   |   |                         |
|---|---|-------------------------|
| Sinusitis bacterial<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Sinusitis bacterial               |                         |
|   | 1 / 168 (0.60%)<br>1                                      | 0 / 170 (0.00%)<br>0    |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Skin infection                    |                         |
|   | 1 / 168 (0.60%)<br>2                                      | 4 / 170 (2.35%)<br>5    |
| Subcutaneous abscess<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Subcutaneous abscess              |                         |
|   | 0 / 168 (0.00%)<br>0                                      | 2 / 170 (1.18%)<br>2    |
| Tinea infection<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Tinea infection                   |                         |
|   | 0 / 168 (0.00%)<br>0                                      | 1 / 170 (0.59%)<br>1    |
| Tinea versicolour<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Tinea versicolour                 |                         |
|   | 1 / 168 (0.60%)<br>1                                      | 0 / 170 (0.00%)<br>0    |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Upper respiratory tract infection |                         |
|   | 17 / 168 (10.12%)<br>20                                   | 19 / 170 (11.18%)<br>30 |
| Tongue fungal infection<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Tongue fungal infection           |                         |
|   | 1 / 168 (0.60%)<br>1                                      | 0 / 170 (0.00%)<br>0    |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Tonsillitis                       |                         |
|   | 3 / 168 (1.79%)<br>3                                      | 3 / 170 (1.76%)<br>5    |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Tooth abscess                     |                         |
|   | 0 / 168 (0.00%)<br>0                                      | 2 / 170 (1.18%)<br>2    |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Tooth infection                   |                         |
|   | 4 / 168 (2.38%)<br>4                                      | 3 / 170 (1.76%)<br>3    |
| Tracheitis<br>subjects affected / exposed<br>occurrences (all)                        | Additional description: Tracheitis                        |                         |
|   | 0 / 168 (0.00%)<br>0                                      | 1 / 170 (0.59%)<br>1    |
| Trichomoniasis<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Trichomoniasis                    |                         |
|   | 1 / 168 (0.60%)<br>1                                      | 0 / 170 (0.00%)<br>0    |

|   |   |                         |
|---|---|-------------------------|
| Tinea pedis<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Tinea pedis                             |                         |
|   | 0 / 168 (0.00%)<br>0  | 1 / 170 (0.59%)<br>1    |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Urinary tract infection                 |                         |
|   | 12 / 168 (7.14%)<br>14  | 20 / 170 (11.76%)<br>41 |
| Vulvovaginal mycotic infection<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Vulvovaginal mycotic infection          |                         |
|   | 1 / 168 (0.60%)<br>1  | 1 / 170 (0.59%)<br>1    |
| Viral diarrhoea<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Viral diarrhoea                         |                         |
|   | 1 / 168 (0.60%)<br>1  | 1 / 170 (0.59%)<br>1    |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Viral infection                         |                         |
|   | 5 / 168 (2.98%)<br>5  | 3 / 170 (1.76%)<br>3    |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Viral upper respiratory tract infection |                         |
|   | 2 / 168 (1.19%)<br>2  | 1 / 170 (0.59%)<br>1    |
| Wound infection bacterial<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Wound infection bacterial               |                         |
|   | 0 / 168 (0.00%)<br>0  | 1 / 170 (0.59%)<br>1    |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Wound infection                         |                         |
|   | 0 / 168 (0.00%)<br>0  | 2 / 170 (1.18%)<br>2    |
| Wound infection pseudomonas<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Wound infection pseudomonas             |                         |
|   | 0 / 168 (0.00%)<br>0  | 1 / 170 (0.59%)<br>1    |
| Metabolism and nutrition disorders  |   |                         |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Decreased appetite                      |                         |
|   | 3 / 168 (1.79%)<br>5  | 3 / 170 (1.76%)<br>3    |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Diabetes mellitus                       |                         |
|   | 0 / 168 (0.00%)<br>0  | 2 / 170 (1.18%)<br>2    |
| Diabetic metabolic decompensation   | Additional description: Diabetic metabolic decompensation       |                         |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Folate deficiency           | Additional description: Folate deficiency        |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 3 / 170 (1.76%) |  |
| occurrences (all)           | 0  | 3               |  |
| Gout                        | Additional description: Gout                     |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                  | 6 / 170 (3.53%) |  |
| occurrences (all)           | 2  | 6               |  |
| Hypercholesterolaemia       | Additional description: Hypercholesterolaemia    |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0  | 3               |  |
| Hypercreatininaemia         | Additional description: Hypercreatininaemia      |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Hyperglycaemia              | Additional description: Hyperglycaemia           |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1  | 1               |  |
| Hyperkalaemia               | Additional description: Hyperkalaemia            |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1  | 1               |  |
| Hyperlipasaemia             | Additional description: Hyperlipasaemia          |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 1  | 1               |  |
| Hyperuricaemia              | Additional description: Hyperuricaemia           |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 3 / 170 (1.76%) |  |
| occurrences (all)           | 0  | 3               |  |
| Hypokalaemia                | Additional description: Hypokalaemia             |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Iron deficiency             | Additional description: Iron deficiency          |                 |  |
| subjects affected / exposed | 1 / 168 (0.60%)                                  | 4 / 170 (2.35%) |  |
| occurrences (all)           | 1  | 4               |  |
| Protein deficiency          | Additional description: Protein deficiency       |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                  | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Type 2 diabetes mellitus    | Additional description: Type 2 diabetes mellitus |                 |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 0 / 168 (0.00%)                                | 2 / 170 (1.18%) |  |
| occurrences (all)           | 0  | 2               |  |
| Vitamin B12 deficiency      | Additional description: Vitamin B12 deficiency |                 |  |
| subjects affected / exposed | 0 / 168 (0.00%)                                | 1 / 170 (0.59%) |  |
| occurrences (all)           | 0  | 1               |  |
| Vitamin D deficiency        | Additional description: Vitamin D deficiency   |                 |  |
| subjects affected / exposed | 3 / 168 (1.79%)                                | 4 / 170 (2.35%) |  |
| occurrences (all)           | 3  | 4               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 15 October 2014  | New Information on Ibrutinib and update of protocol and PIC following IB V8.0   |
| 04 February 2015 | Adaption of sample size calculation with respect to current recruitment rate  |
| 15 July 2015     | Changes in the protocol, following DSMB recommendation to prohibit concomitant medication with Xa-Inhibitors, alternatively to allow heparines only.                |
| 13 January 2016  | New Information on Ibrutinib and update of protocol and PIC following IB V9.0;Adaption of statistical assumption to allow confirmatory analyses of overall survival |
| 08 July 2016     | New safety information on interstitial lung disease, amendment of PIC accordingly   |
| 28 March 2017    | New Information on Ibrutinib and update of protocol and PIC following IB V10.0  |
| 26 June 2017     | New Information on Ibrutinib and update of protocol and PIC following SmPC Februar 2017; administrative changes   |
| 09 April 2018    | New Information on Ibrutinib and update of protocol and PIC following SmPC August 2017; Adaption of analysis time points and details of statistical analyses        |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34758069>