



## Clinical trial results:

### Phase III trial of combined immunochemotherapy with Fludarabine, Cyclophosphamide and Rituximab (FCR) versus Bendamustine and Rituximab (BR) in patients with previously untreated chronic lymphocytic leukemia

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2007-007587-21  |
| Trial protocol           | DE AT DK CZ     |
| Global end of trial date | 01 January 2018 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 21 August 2020 |
| First version publication date | 21 August 2020 |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | CLL10 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00769522 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | German CLL Study Group, University Hospital Cologne                               |
| Sponsor organisation address | Gleuelerstr. 176-178, Cologne, Germany, 50935                                     |
| Public contact               | Information Desk, German CLL Study Group, +49 22147888198, cll-studie@uk-koeln.de |
| Scientific contact           | Information Desk, German CLL Study Group, +49 22147888198, cll-studie@uk-koeln.de |

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                       | 12 March 2019    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 29 December 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 January 2018  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective is to demonstrate that BR has a non-inferior therapeutic efficacy compared with FCR, but a better safety profile causing less myelosuppression, infections and secondary neoplasias.

Protection of trial subjects:

For a prevention of an anaphylactic reaction and a cytokine release Syndrome patients should be pretreated with antihistamines, Paracetamol/Acetaminophen and Prednisolon.

In case of a leukocytopenia CTC grade 3 or 4 with a Duration of >7 days, prophylaxis of pneumocystis carinii-pneumonia is recommended. Other routine measures such as antibiotic, antimycotic or viostatic prophylaxis as well as the use of growth factors should be given if clinically indicated.

Background therapy:

Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR) is the Standard therapy for physically fit patients with advanced chronic lymphocytic leukaemia and Background therapy in the CLL10-trial.

Following the results of a Phase 2 study by the MD Anderson Cancer Center and a Phase 3 Study by the German CLL-Study Group, the CLL8 study, FCR has become the Standard front-line therapy for physically fit patients with chronic lymphocytic leukemia. However this Regimen is associated with substantial toxic effects, most importantly severe haematotoxicity in 56% of patients and severe infections in 25% of patients during treatment. A Long-term follow-up of patients treated with FCR showed prolonged neutropenia in 17-35% and an elevated risk of secondary neoplasia.

Evidence for comparator:

Chemoimmunotherapy with bendamustine and rituximab (BR) is the comparator. The combination of the alkylating Agent bendamustine and rituximab has shown promising results in a Phase 2 study in front-line therapy of chronic lymphocytic leukaemia with Overall responses in 103 of 117 patients and complete responses in 27 of 117 patients. Event-free survival of 34 months and low incidence of severe neutropenia (20%) and infections (8%) led to the hypothesis that the treatment with BR might be similarly effective but less toxic compared with the Standard treatment FCR.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 02 October 2008  |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 6 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Austria: 10       |
| Country: Number of subjects enrolled | Czech Republic: 4 |
| Country: Number of subjects enrolled | Denmark: 24       |
| Country: Number of subjects enrolled | Germany: 487      |
| Country: Number of subjects enrolled | Switzerland: 36   |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 561 |
| EEA total number of subjects       | 525 |

Notes:

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**Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 353 |
| From 65 to 84 years                       | 208 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

564 patients were enrolled between 10/2008 and 04/2012. The patients were randomly assigned to FCR (284) and BR (280) .

561 patients were allocated to treatment because 3 patients dropped off during the randomisation process. 282 patients were allocated to FCR and 279 patients were allocated to BR (baseline values).

### Pre-assignment

Screening details:

688 treatment-naïve patients diagnosed with CLL were registered for central screening . The central screening was performed by the GCLLSG central study office in Cologne, Germany and included immunophenotyping, FISH, evaluation of the comorbidity and renal function. 127 patients were not eligible for participation.

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 688 <sup>[1]</sup> |
| Number of subjects completed | 561                |

### Pre-assignment subject non-completion reasons

|                            |                         |
|----------------------------|-------------------------|
| Reason: Number of subjects | Protocol deviation: 127 |
|----------------------------|-------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All patients who meet the eligibility criteria for study entry can be enrolled into the trial. To verify the eligibility of patients, a patient screening by a medical review of the pretherapeutic staging as well as a central immunophenotyping for confirmation of the diagnosis and FISH analysis to exclude patients with a 17p deletion or mutation will be performed before randomization.

688 patients started pre-assignment period. 127 patients were assessed as Screening failures. 561 completed.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes                                    |
| <b>Arm title</b>             | Fludarabine/Cyclophosphamide/Rituximab |

Arm description:

Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Standard                          |
| Investigational medicinal product name | Fludarabine                       |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Cycle 1-6 on days 1-3: 25mg/m2

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Cyclophosphamide                 |
| Investigational medicinal product code |                                  |
| Other name                             | Cytosan                          |
| Pharmaceutical forms                   | Powder for solution for infusion |

|   |                       |
|---|-----------------------|
| Routes of administration  | Intravenous use       |
| Dosage and administration details:<br>250 mg/m <sup>2</sup> cycle 1-6 on days 1, 2, 3.  |                       |
| Investigational medicinal product name  | Rituximab             |
| Investigational medicinal product code  |                       |
| Other name  | Rituxan, Truxima      |
| Pharmaceutical forms  | Solution for infusion |
| Routes of administration  | Intravenous use       |
| Dosage and administration details:<br>Cycle 1: 375 mg/ m <sup>2</sup> i.v. on day 0<br>Cycles 2-6: 500 mg/ m <sup>2</sup> i.v. on day 1 (before FC) |                       |

|   |                                   |
|---|-----------------------------------|
| <b>Arm title</b>  | Bendamustine/Rituximab            |
| Arm description:<br>Chemoimmunotherapy with bendamustine and rituximab  |                                   |
| Arm type  | Active comparator                 |
| Investigational medicinal product name  | Bendamustine                      |
| Investigational medicinal product code  |                                   |
| Other name  | Ribomustin, Treanda               |
| Pharmaceutical forms  | Powder for solution for injection |
| Routes of administration  | Intravenous use                   |
| Dosage and administration details:<br>90 mg/m <sup>2</sup> course 1-6, days 1 and 2   |                                   |
| Investigational medicinal product name  | Rituximab                         |
| Investigational medicinal product code  |                                   |
| Other name  | Rituxan, Truxima                  |
| Pharmaceutical forms  | Solution for infusion             |
| Routes of administration  | Intravenous use                   |
| Dosage and administration details:<br>Cycle1: 375mg/m <sup>2</sup> i.v. on day 0<br>cycles 2-6: 500 mg/m <sup>2</sup> i.v. on day 1 (before FC) |                                   |

| <b>Number of subjects in period 1</b>           | Fludarabine/Cyclophosphamide/Rituximab | Bendamustine/Rituximab |
|---|--|------------------------|
| Started   | 282                                    | 279                    |
| treatment allocation                            | 282                                    | 279                    |
| treatment                                       | 282                                    | 279                    |
| follow-up                                       | 282                                    | 279                    |
| Completed                                       | 199                                    | 224                    |
| Not completed                                   | 83                                     | 55                     |
| Adverse event, serious fatal                    | 3                                      | 1                      |
| withdrawal of consent before start of treatment | 3                                      | 1                      |
| Adverse event, non-fatal                        | 65                                     | 38                     |
| various reasons                                 | 10                                     | 14                     |
| Lack of efficacy                                | 2                                      | 1                      |



## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Fludarabine/Cyclophosphamide/Rituximab |
| Reporting group description:<br>Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab. |  |
| Reporting group title  | Bendamustine/Rituximab                 |
| Reporting group description:<br>Chemoimmunotherapy with bendamustine and rituximab                   |  |

| Reporting group values                               | Fludarabine/Cyclophosphamide/Rituximab | Bendamustine/Rituximab | Total |
|--|--|------------------------|-------|
| Number of subjects                                   | 282                                    | 279                    | 561   |
| Age categorical                                      |  |                        |       |
| Median Age 60.5 years for FCR and 62.0 years for BR. |  |                        |       |
| Units: Subjects                                      |  |                        |       |
| Adults (18-64 years)                                 | 187                                    | 166                    | 353   |
| 65 years and over                                    | 95                                     | 113                    | 208   |
| Age continuous                                       |  |                        |       |
| Units: years   |  |                        |       |
| median   | 60.5                                   | 62                     | -     |
| inter-quartile range (Q1-Q3)                         | 55 to 67                               | 54 to 69               | -     |
| Gender categorical                                   |  |                        |       |
| Units: Subjects                                      |  |                        |       |
| Female   | 81                                     | 72                     | 153   |
| Male   | 201                                    | 207                    | 408   |

### Subject analysis sets

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | CLL10 Clinical Study Report |
| Subject analysis set type  | Intention-to-treat          |

Subject analysis set description:

The intent-to-treat population (ITT) included all randomized subjects. 561 Patients (282 patients in the FCR arm and 279 patients in the BR arm) were assessed for progression free survival PFS (primary endpoint). PFS was measured from the date of randomization to the date of first documented disease progression (as defined by the IWCLL 2008 response criteria) or death by any cause, whichever occurred first. Following secondary endpoints were assessed: duration of Remission, event free survival (EFS), overall survival (OS), MRD, complete response rates and partial remission rates, response rates and survival times in biological subgroups, rates of toxicities and quality of life.

| Reporting group values                               | CLL10 Clinical Study Report |  |  |
|--|-----------------------------|--|--|
| Number of subjects                                   | 561                         |  |  |
| Age categorical                                      |                             |  |  |
| Median Age 60.5 years for FCR and 62.0 years for BR. |                             |  |  |
| Units: Subjects                                      |                             |  |  |
| Adults (18-64 years)                                 | 353                         |  |  |
| 65 years and over                                    | 208                         |  |  |

|                              |              |  |  |
|------------------------------|--------------|--|--|
| Age continuous               |              |  |  |
| Units: years                 |              |  |  |
| median                       | 61           |  |  |
| inter-quartile range (Q1-Q3) | 54.5 to 68.0 |  |  |
| Gender categorical           |              |  |  |
| Units: Subjects              |              |  |  |
| Female                       | 153          |  |  |
| Male                         | 408          |  |  |



## End points

### End points reporting groups

|                                   |   |
|-----------------------------------|---|
| Reporting group title             | Fludarabine/Cyclophosphamide/Rituximab  |
| Reporting group description:      | Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab.  |
| Reporting group title             | Bendamustine/Rituximab  |
| Reporting group description:      | Chemoimmunotherapy with bendamustine and rituximab  |
| Subject analysis set title        | CLL10 Clinical Study Report   |
| Subject analysis set type         | Intention-to-treat  |
| Subject analysis set description: | The intent-to-treat population (ITT) included all randomized subjects. 561 Patients (282 patients in the FCR arm and 279 patients in the BR arm) were assessed for progression free survival PFS (primary endpoint). PFS was measured from the date of randomization to the date of first documented disease progression (as defined by the IWCLL 2008 response criteria) or death by any cause, whichever occurred first. Following secondary endpoints were assessed:<br>duration of Remission, event free survival (EFS), overall survival (OS), MRD, complete response rates and partial remission rates, response rates and survival times in biological subgroups, rates of toxicities and quality of life. |

### Primary: Progression Free Survival (PFS)

|                        |   |
|------------------------|---|
| End point title        | Progression Free Survival (PFS)   |
| End point description: | Progression free survival will be calculated as the time between date of randomization and date of progression or death of any cause. |
| End point type         | Primary   |
| End point timeframe:   | The progression free survival (PFS) rate after 24 months  |

| End point values              | Fludarabine/Cyclophosphamide/Rituximab | Bendamustine/Rituximab | CLL10 Clinical Study Report |  |
|-------------------------------|--|------------------------|-----------------------------|--|
| Subject group type            | Reporting group                        | Reporting group        | Subject analysis set        |  |
| Number of subjects analysed   | 282                                    | 279                    | 561                         |  |
| Units: PFS rates at 24 months |  |                        |                             |  |
| number (not applicable)       | 84.3                                   | 77.8                   | 81.0                        |  |

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| Statistical analysis title        | Statistical plan for primary endpoint  |
| Statistical analysis description: | Progression-free survival (PFS) is defined as the time from randomization to disease progression or death from any cause. These will be counted as events for PFS. Patients who have neither progressed nor died will be censored.<br>A Cox proportional hazard model will be applied on progression-free survival time including the variables for study medication and the stratification parameters as covariates. If the upper limit of the 90.4%-confidence interval of the hazard-ratio of BR compared to FCR is |
| Comparison groups                 | Fludarabine/Cyclophosphamide/Rituximab v   |

|   |                                |
|---|--------------------------------|
|   | Bendamustine/Rituximab         |
| Number of subjects included in analysis | 561                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| P-value                                 | < 0.001 <sup>[2]</sup>         |
| Method                                  | Regression, Cox                |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 1.643                          |
| Confidence interval                     |                                |
| level                                   | 90.4 %                         |
| sides                                   | 1-sided                        |
| upper limit                             | 2.064                          |

Notes:

[1] - The significance level of the study is 5% (one-sided, with one interim analysis and one final analysis using the method of O'Brien and Fleming to allocate the global 5% significance level to the 2 analyses), the significance level of the final analysis is accordingly 4.8%. The power is 80%. The CLL 10 protocol is a non-inferiority trial. The expected PFS 2 years after start of FCR therapy is 75% which translates to an exponential parameter of 0.1438.

[2] - A p value < 0.001 and an upper limit of the 90.4% confidence interval is greater than 1.388. Thus, the null hypothesis for the corresponding non-inferiority hypothesis cannot be rejected according to the protocol.

## 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 | Chemoimmunotherapy BR |
|-----------------------|-----------------------|

Reporting group description: -

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Chemoimmunotherapy FCR |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events  | Chemoimmunotherapy BR                           | Chemoimmunotherapy FCR |  |
|---|---|------------------------|--|
| Total subjects affected by serious adverse events                   |   |                        |  |
| subjects affected / exposed   | 135 / 278 (48.56%)                              | 155 / 279 (55.56%)     |  |
| number of deaths (all causes)                                       | 78  | 69                     |  |
| number of deaths resulting from adverse events                      | 14  | 20                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                        |  |
| Acute myeloid leukaemia   | Additional description: Acute myeloid leukaemia |                        |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                 | 4 / 279 (1.43%)        |  |
| occurrences causally related to treatment / all                     | 0 / 1   | 4 / 4                  |  |
| deaths causally related to treatment / all                          | 0 / 0   | 3 / 3                  |  |
| Adenocarcinoma  | Additional description: Adenocarcinoma          |                        |  |
| subjects affected / exposed   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%)        |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 1                  |  |
| Basal cell carcinoma  | Additional description: Basal cell carcinoma    |                        |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                 | 4 / 279 (1.43%)        |  |
| occurrences causally related to treatment / all                     | 1 / 1   | 1 / 4                  |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                  |  |
| Bladder cancer  | Additional description: Bladder cancer          |                        |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Bladder neoplasm                                | Additional description: Bladder neoplasm                 |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Breast cancer                                   | Additional description: Breast cancer                    |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Bronchial carcinoma                             | Additional description: Bronchial carcinoma              |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0           |  |
| Breast cancer female                            | Additional description: Breast cancer female             |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Clear cell sarcoma of the kidney                | Additional description: Clear cell sarcoma of the kidney |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Colon cancer metastatic                         | Additional description: Colon cancer metastatic          |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Colorectal cancer                               | Additional description: Colorectal cancer                |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1           |  |
| Glioblastoma                                    | Additional description: Glioblastoma                     |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Malignant melanoma                              | Additional description: Malignant melanoma                          |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Malignant neoplasm of unknown primary site      | Additional description: Malignant neoplasm of unknown primary site  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Myelodysplastic syndrome                        | Additional description: Myelodysplastic syndrome                    |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 4 / 279 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 4 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Metastatic neoplasm                             | Additional description: Metastatic neoplasm                         |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Oesophageal adenocarcinoma                      | Additional description: Oesophageal adenocarcinoma                  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Prostate cancer                                 | Additional description: Prostate cancer                             |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Rectal cancer                                   | Additional description: Rectal cancer                               |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Refractory anaemia with an excess of blasts     | Additional description: Refractory anaemia with an excess of blasts |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Skin cancer                                     | Additional description: Skin cancer                     |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Squamous cell carcinoma of skin                 | Additional description: Squamous cell carcinoma of skin |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Thyroid cancer                                  | Additional description: Thyroid cancer                  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Transitional cell carcinoma                     | Additional description: Transitional cell carcinoma     |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Vascular disorders                              |   |                 |  |
| Aortic aneurysm                                 | Additional description: Aortic aneurysm                 |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Deep vein thrombosis                            | Additional description: Deep vein thrombosis            |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hypertension                                    | Additional description: Hypertension                    |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Intermittent claudication                       | Additional description: Intermittent claudication       |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Peripheral artery stenosis                      | Additional description: Peripheral artery stenosis    |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Thrombophlebitis                                | Additional description: Thrombophlebitis              |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Surgical and medical procedures                 |   |                 |  |
| Hernia repair                                   | Additional description: Hernia repair                 |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                                       | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hip arthroplasty                                | Additional description: Hip arthroplasty              |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hip surgery                                     | Additional description: Hip surgery                   |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Intervertebral disc operation                   | Additional description: Intervertebral disc operation |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Knee operation                                  | Additional description: Knee operation                |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lung lobectomy                                  | Additional description: Lung lobectomy                |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Meniscus operation                              | Additional description: Meniscus operation          |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                     | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Oesophagectomy                                  | Additional description: Oesophagectomy              |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                     | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 1 / 1           |  |
| Osteotomy                                       | Additional description: Osteotomy                   |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Penile prosthesis insertion                     | Additional description: Penile prosthesis insertion |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Prostatectomy                                   | Additional description: Prostatectomy               |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Spinal operation                                | Additional description: Spinal operation            |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Spinal laminectomy                              | Additional description: Spinal laminectomy          |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Spinal decompression                            | Additional description: Spinal decompression        |                 |  |



|  |   |                  |  |
|--|---|------------------|--|
| subjects affected / exposed                          | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0            |  |
| Thyroidectomy  | Additional description: Thyroidectomy             |                  |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)                                   | 0 / 279 (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                          | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%)  |  |
| occurrences causally related to treatment / all      | 0 / 1   | 1 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0            |  |
| Death  | Additional description: Death                     |                  |  |
| subjects affected / exposed                          | 0 / 278 (0.00%)                                   | 2 / 279 (0.72%)  |  |
| occurrences causally related to treatment / all      | 0 / 0   | 1 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0   | 1 / 2            |  |
| Pyrexia  | Additional description: Pyrexia                   |                  |  |
| subjects affected / exposed                          | 17 / 278 (6.12%)                                  | 15 / 279 (5.38%) |  |
| occurrences causally related to treatment / all      | 14 / 17   | 17 / 19          |  |
| deaths causally related to treatment / all           | 0 / 0   | 1 / 1            |  |
| Immune system disorders                              |   |                  |  |
| Anaphylactic reaction                                | Additional description: Anaphylactic reaction     |                  |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%)  |  |
| occurrences causally related to treatment / all      | 1 / 1   | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0            |  |
| Anaphylactic shock                                   | Additional description: Anaphylactic shock        |                  |  |
| subjects affected / exposed                          | 2 / 278 (0.72%)                                   | 0 / 279 (0.00%)  |  |
| occurrences causally related to treatment / all      | 2 / 2   | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0            |  |
| Cytokine release syndrome                            | Additional description: Cytokine release syndrome |                  |  |
| subjects affected / exposed                          | 4 / 278 (1.44%)                                   | 2 / 279 (0.72%)  |  |
| occurrences causally related to treatment / all      | 4 / 4   | 2 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0            |  |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| Drug hypersensitivity                           | Additional description: Drug hypersensitivity        |                 |                 |
|   | subjects affected / exposed                          | 3 / 278 (1.08%) | 0 / 279 (0.00%) |
|   | occurrences causally related to treatment / all      | 2 / 3           | 0 / 0           |
|   | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Hypersensitivity                                | Additional description: Hypersensitivity             |                 |                 |
|   | subjects affected / exposed                          | 7 / 278 (2.52%) | 2 / 279 (0.72%) |
|   | occurrences causally related to treatment / all      | 7 / 7           | 2 / 2           |
|   | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Serum sickness                                  | Additional description: Serum sickness               |                 |                 |
|   | subjects affected / exposed                          | 1 / 278 (0.36%) | 0 / 279 (0.00%) |
|   | occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |
|   | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |  |                 |                 |
|   | Additional description: Benign prostatic hyperplasia |                 |                 |
|   | subjects affected / exposed                          | 0 / 278 (0.00%) | 1 / 279 (0.36%) |
|   | occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |
| Calculus prostatic                              | Additional description: Calculus prostatic           |                 |                 |
|   | subjects affected / exposed                          | 1 / 278 (0.36%) | 0 / 279 (0.00%) |
|   | occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |
|   | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Prostatitis                                     | Additional description: Prostatitis                  |                 |                 |
|   | subjects affected / exposed                          | 1 / 278 (0.36%) | 0 / 279 (0.00%) |
|   | occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |
|   | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |  |                 |                 |
|   | Additional description: Aspiration                   |                 |                 |
|   | subjects affected / exposed                          | 0 / 278 (0.00%) | 1 / 279 (0.36%) |
|   | occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |
| Asthma  |  |                 |                 |
|   | Additional description: Asthma                       |                 |                 |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bronchial haemorrhage                           | Additional description: Bronchial haemorrhage |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Chylothorax                                     | Additional description: Chylothorax           |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Epistaxis                                       | Additional description: Epistaxis             |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hiccups   | Additional description: Hiccups               |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lung infiltration                               | Additional description: Lung infiltration     |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pleural effusion                                | Additional description: Pleural effusion      |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pneumonitis                                     | Additional description: Pneumonitis           |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pneumothorax                                    | Additional description: Pneumothorax          |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pulmonary embolism                              | Additional description: Pulmonary embolism     |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)                                | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 4  | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0           |  |
| Pulmonary sarcoidosis                           | Additional description: Pulmonary sarcoidosis  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Respiratory disorder                            | Additional description: Respiratory disorder   |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Psychiatric disorders                           |  |                 |  |
| Alcoholism                                      | Additional description: Alcoholism             |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Acute psychosis                                 | Additional description: Acute psychosis        |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Investigations                                  |  |                 |  |
| Arthroscopy                                     | Additional description: Arthroscopy            |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Biopsy adrenal gland                            | Additional description: Biopsy adrenal gland   |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Blood sodium decreased                          | Additional description: Blood sodium decreased |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Investigation                                   | Additional description: Investigation                 |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Neutrophil count                                | Additional description: Neutrophil count              |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Transaminases increased                         | Additional description: Transaminases increased       |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Injury, poisoning and procedural complications  |   |                 |  |
| Allergic transfusion reaction                   | Additional description: Allergic transfusion reaction |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Ankle fracture                                  | Additional description: Ankle fracture                |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Arterial injury                                 | Additional description: Arterial injury               |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Cervical vertebral fracture                     | Additional description: Cervical vertebral fracture   |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Fall  | Additional description: Fall                          |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Femoral neck fracture                           | Additional description: Femoral neck fracture      |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                    | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Foot fracture                                   | Additional description: Foot fracture              |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                    | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Infusion related reaction                       | Additional description: Infusion related reaction  |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)                                    | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 4 / 4  | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Post procedural haematuria                      | Additional description: Post procedural haematuria |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Road traffic accident                           | Additional description: Road traffic accident      |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Tendon rupture                                  | Additional description: Tendon rupture             |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Transfusion reaction                            | Additional description: Transfusion reaction       |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cardiac disorders                               |  |                 |  |
| Acute coronary syndrome                         | Additional description: Acute coronary syndrome    |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Acute myocardial infarction                     | Additional description: Acute myocardial infarction |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)                                     | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 3   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Arrhythmia                                      | Additional description: Arrhythmia                  |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Atrial fibrillation                             | Additional description: Atrial fibrillation         |                 |  |
| subjects affected / exposed                     | 4 / 278 (1.44%)                                     | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 4   | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Atrial flutter                                  | Additional description: Atrial flutter              |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Atrial tachycardia                              | Additional description: Atrial tachycardia          |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bradyarrhythmia                                 | Additional description: Bradyarrhythmia             |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                     | 1 / 279 (0.36%) |  |
| 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                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Coronary artery dilatation                      | Additional description: Coronary artery dilatation  |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 1 / 278 (0.36%)                                 | 0 / 279 (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                     | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Myocardial infarction                           | Additional description: Myocardial infarction   |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)                                 | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 1 / 3   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Myocardial ischaemia                            | Additional description: Myocardial ischaemia    |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                 | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Pericardial effusion                            | Additional description: Pericardial effusion    |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Tachycardia                                     | Additional description: Tachycardia             |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Tachyarrhythmia                                 | Additional description: Tachyarrhythmia         |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Nervous system disorders                        |   |                 |  |
| Cerebellar ischaemia                            | Additional description: Cerebellar ischaemia    |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Cerebral ischaemia                              | Additional description: Cerebral ischaemia      |                 |  |



|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 2 / 278 (0.72%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Diabetic hyperosmolar coma                      | Additional description: Diabetic hyperosmolar coma |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                    | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Dizziness                                       | Additional description: Dizziness                  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Horner's syndrome                               | Additional description: Horner's syndrome          |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Leukoencephalopathy                             | Additional description: Leukoencephalopathy        |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Paraesthesia                                    | Additional description: Paraesthesia               |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                    | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Syncope   | Additional description: Syncope                    |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)                                    | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 3  | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Transient ischaemic attack                      | Additional description: Transient ischaemic attack |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                                    | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Blood and lymphatic system disorders            |  |                 |  |
| Anaemia   | Additional description: Anaemia                    |                 |  |

|   |   |                  |  |
|---|---|------------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                                     | 6 / 279 (2.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0   | 6 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Febrile neutropenia                             | Additional description: Febrile neutropenia         |                  |  |
| subjects affected / exposed                     | 13 / 278 (4.68%)                                    | 18 / 279 (6.45%) |  |
| occurrences causally related to treatment / all | 11 / 13   | 18 / 19          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Febrile bone marrow aplasia                     | Additional description: Febrile bone marrow aplasia |                  |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Haemolysis                                      | Additional description: Haemolysis                  |                  |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 2 / 279 (0.72%)  |  |
| occurrences causally related to treatment / all | 1 / 1   | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Haemolytic anaemia                              | Additional description: Haemolytic anaemia          |                  |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                                     | 0 / 279 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2   | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Leukopenia                                      | Additional description: Leukopenia                  |                  |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 0 / 279 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Neutropenia                                     | Additional description: Neutropenia                 |                  |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                     | 4 / 279 (1.43%)  |  |
| occurrences causally related to treatment / all | 1 / 1   | 4 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Pancytopenia                                    | Additional description: Pancytopenia                |                  |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                     | 2 / 279 (0.72%)  |  |
| occurrences causally related to treatment / all | 0 / 0   | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Platelet disorder                               | Additional description: Platelet disorder           |                  |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Thrombocytopenia                                | Additional description: Thrombocytopenia    |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Ear and labyrinth disorders                     |   |                 |  |
| Vertigo positional                              | Additional description: Vertigo positional  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Eye disorders                                   |   |                 |  |
| Retinal detachment                              | Additional description: Retinal detachment  |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Gastrointestinal disorders                      |   |                 |  |
| Abdominal pain                                  | Additional description: Abdominal pain      |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                             | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Acute abdomen                                   | Additional description: Acute abdomen       |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Aphthous stomatitis                             | Additional description: Aphthous stomatitis |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Constipation                                    | Additional description: Constipation        |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 1                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |

|   |  |                 |  |
|---|--|-----------------|--|
| Diarrhoea                                       | Additional description: Diarrhoea                        |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Diverticulum                                    | Additional description: Diverticulum                     |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Gastritis erosive                               | Additional description: Gastritis erosive                |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Gastrooesophageal reflux disease                | Additional description: Gastrooesophageal reflux disease |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (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                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Large intestine perforation                     | Additional description: Large intestine perforation      |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Nausea  | Additional description: Nausea                           |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neutropenic colitis                             | Additional description: Neutropenic colitis              |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 1 / 1           |  |
| Pancreatitis                                    | Additional description: Pancreatitis                     |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Vomiting  | Additional description: Vomiting            |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                             | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 2 / 3                                       | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Hepatobiliary disorders                         |   |                 |  |
| Cholelithiasis                                  | Additional description: Cholelithiasis      |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Cholangiolitis                                  | Additional description: Cholangiolitis      |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Hepatitis toxic                                 | Additional description: Hepatitis toxic     |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                             | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Hepatotoxicity                                  | Additional description: Hepatotoxicity      |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                             | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |   |                 |  |
| Dermatitis allergic                             | Additional description: Dermatitis allergic |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                             | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 2 / 2                                       | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Eczema  | Additional description: Eczema              |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                             | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                       | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           |  |
| Erythema  | Additional description: Erythema            |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 278 (0.36%)                                      | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Hyperkeratosis                                  | Additional description: Hyperkeratosis               |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                      | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Leukoplakia                                     | Additional description: Leukoplakia                  |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                      | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Rash  | Additional description: Rash                         |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                      | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Rash generalised                                | Additional description: Rash generalised             |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                      | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Toxic epidermal necrolysis                      | Additional description: Toxic epidermal necrolysis   |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                                      | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Renal and urinary disorders                     |  |                 |  |
| Bladder malposition acquired                    | Additional description: Bladder malposition acquired |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                      | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Calculus ureteric                               | Additional description: Calculus ureteric            |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                      | 1 / 279 (0.36%) |  |
| 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                     | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |   |                 |  |
| Arthritis                                       | Additional description: Arthritis                 |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Arthrofibrosis                                  | Additional description: Arthrofibrosis            |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Back pain                                       | Additional description: Back pain                 |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Osteoarthritis                                  | Additional description: Osteoarthritis            |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infections and infestations                     |   |                 |  |
| Abscess of salivary gland                       | Additional description: Abscess of salivary gland |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Anal abscess                                    | Additional description: Anal abscess              |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bacterial sepsis                                | Additional description: Bacterial sepsis          |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |

|                                |  |                 |                 |
|--------------------------------|--|-----------------|-----------------|
| Bacterial infection            | Additional description: Bacterial infection            |                 |                 |
|                                | subjects affected / exposed                            | 0 / 278 (0.00%) | 1 / 279 (0.36%) |
|                                | 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                            | 3 / 278 (1.08%) | 6 / 279 (2.15%) |
|                                | occurrences causally related to treatment / all        | 0 / 4           | 3 / 7           |
|                                | deaths causally related to treatment / all             | 0 / 1           | 0 / 0           |
| Bronchopneumonia               | Additional description: Bronchopneumonia               |                 |                 |
|                                | subjects affected / exposed                            | 3 / 278 (1.08%) | 3 / 279 (1.08%) |
|                                | occurrences causally related to treatment / all        | 1 / 3           | 1 / 4           |
|                                | deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |
| Bronchopulmonary aspergillosis | Additional description: Bronchopulmonary aspergillosis |                 |                 |
|                                | subjects affected / exposed                            | 0 / 278 (0.00%) | 1 / 279 (0.36%) |
|                                | occurrences causally related to treatment / all        | 0 / 0           | 1 / 1           |
|                                | deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |
| Cellulitis                     | Additional description: Cellulitis                     |                 |                 |
|                                | subjects affected / exposed                            | 1 / 278 (0.36%) | 0 / 279 (0.00%) |
|                                | occurrences causally related to treatment / all        | 1 / 1           | 0 / 0           |
|                                | deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |
| Chronic sinusitis              | Additional description: Chronic sinusitis              |                 |                 |
|                                | subjects affected / exposed                            | 0 / 278 (0.00%) | 1 / 279 (0.36%) |
|                                | occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           |
|                                | deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |
| Clostridium difficile sepsis   | Additional description: Clostridium difficile sepsis   |                 |                 |
|                                | subjects affected / exposed                            | 0 / 278 (0.00%) | 1 / 279 (0.36%) |
|                                | occurrences causally related to treatment / all        | 0 / 0           | 1 / 1           |
|                                | deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |
| Cystitis                       | Additional description: Cystitis                       |                 |                 |
|                                | subjects affected / exposed                            | 0 / 278 (0.00%) | 2 / 279 (0.72%) |
|                                | occurrences causally related to treatment / all        | 0 / 0           | 2 / 2           |
|                                | deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |
| Diverticulitis                 | Additional description: Diverticulitis                 |                 |                 |
|                                |  |                 |                 |



|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 2 / 278 (0.72%)   | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 2 / 2   | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Erysipelas                                      | Additional description: Erysipelas                          |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Escherichia urinary tract infection             | Additional description: Escherichia urinary tract infection |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Febrile infection                               | Additional description: Febrile infection                   |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)   | 6 / 279 (2.15%) |  |
| occurrences causally related to treatment / all | 3 / 3   | 4 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastroenteritis                                 | Additional description: Gastroenteritis                     |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastroenteritis clostridial                     | Additional description: Gastroenteritis clostridial         |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastrointestinal infection                      | Additional description: Gastrointestinal infection          |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastroenteritis norovirus                       | Additional description: Gastroenteritis norovirus           |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Genital herpes                                  | Additional description: Genital herpes                      |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| H1N1 influenza                                  | Additional description: H1N1 influenza        |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hepatitis B                                     | Additional description: Hepatitis B           |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 1 / 1           |  |
| Herpes zoster                                   | Additional description: Herpes zoster         |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)                               | 9 / 279 (3.23%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 3 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Herpes zoster oticus                            | Additional description: Herpes zoster oticus  |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Influenza                                       | Additional description: Influenza             |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infection                                       | Additional description: Infection             |                 |  |
| subjects affected / exposed                     | 3 / 278 (1.08%)                               | 4 / 279 (1.43%) |  |
| occurrences causally related to treatment / all | 5 / 6   | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Lung infection                                  | Additional description: Lung infection        |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                               | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Neutropenic infection                           | Additional description: Neutropenic infection |                 |  |

|   |  |                  |  |
|---|--|------------------|--|
| subjects affected / exposed                     | 4 / 278 (1.44%)  | 3 / 279 (1.08%)  |  |
| occurrences causally related to treatment / all | 4 / 4  | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Neutropenic sepsis                              | Additional description: Neutropenic sepsis               |                  |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Oesophageal candidiasis                         | Additional description: Oesophageal candidiasis          |                  |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Pharyngitis                                     | Additional description: Pharyngitis                      |                  |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Pleural infection                               | Additional description: Pleural infection                |                  |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Pneumocystis jirovecii pneumonia                | Additional description: Pneumocystis jirovecii pneumonia |                  |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 2 / 279 (0.72%)  |  |
| occurrences causally related to treatment / all | 1 / 1  | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Pneumonia bacterial                             | Additional description: Pneumonia bacterial              |                  |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%)  |  |
| 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                     | 21 / 278 (7.55%)   | 25 / 279 (8.96%) |  |
| occurrences causally related to treatment / all | 13 / 22  | 16 / 31          |  |
| deaths causally related to treatment / all      | 2 / 2  | 1 / 2            |  |
| Pneumonia haemophilus                           | Additional description: Pneumonia haemophilus            |                  |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pneumonia mycoplasmal                           | Additional description: Pneumonia mycoplasmal                      |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pneumonia pneumococcal                          | Additional description: Pneumonia pneumococcal                     |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pneumonia viral                                 | Additional description: Pneumonia viral                            |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Post procedural sepsis                          | Additional description: Post procedural sepsis                     |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1  | 0 / 0           |  |
| Progressive multifocal leukoencephalopathy      | Additional description: Progressive multifocal leukoencephalopathy |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1  | 0 / 0           |  |
| Pulmonary sepsis                                | Additional description: Pulmonary sepsis                           |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0  | 1 / 2           |  |
| Respiratory tract infection                     | Additional description: Respiratory tract infection                |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Rhinovirus infection                            | Additional description: Rhinovirus infection                       |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Scrotal abscess                                 | Additional description: Scrotal abscess                   |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| 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                     | 3 / 278 (1.08%)   | 5 / 279 (1.79%) |  |
| occurrences causally related to treatment / all | 1 / 3   | 3 / 5           |  |
| deaths causally related to treatment / all      | 1 / 2   | 2 / 2           |  |
| Sinobronchitis                                  | Additional description: Sinobronchitis                    |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Sinusitis                                       | Additional description: Sinusitis                         |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)   | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Soft tissue infection                           | Additional description: Soft tissue infection             |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Tonsillitis                                     | Additional description: Tonsillitis                       |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)   | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Urinary tract infection                         | Additional description: Urinary tract infection           |                 |  |
| subjects affected / exposed                     | 2 / 278 (0.72%)   | 7 / 279 (2.51%) |  |
| occurrences causally related to treatment / all | 2 / 2   | 3 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Upper respiratory tract infection               | Additional description: Upper respiratory tract infection |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 3 / 278 (1.08%)                         | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 3                                   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           |  |
| Urosepsis                                       | Additional description: Urosepsis       |                 |  |
| subjects affected / exposed                     | 0 / 278 (0.00%)                         | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0                                   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           |  |
| Metabolism and nutrition disorders              |   |                 |  |
| Hyperglycaemia                                  | Additional description: Hyperglycaemia  |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                         | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1                                   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           |  |
| Lactic acidosis                                 | Additional description: Lactic acidosis |                 |  |
| subjects affected / exposed                     | 1 / 278 (0.36%)                         | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                   | Chemoimmunotherapy BR                        | Chemoimmunotherapy FCR |  |
|---|--|------------------------|--|
| Total subjects affected by non-serious adverse events               |  |                        |  |
| subjects affected / exposed   | 248 / 278 (89.21%)                           | 271 / 279 (97.13%)     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                        |  |
| Basal cell carcinoma  | Additional description: Basal cell carcinoma |                        |  |
| subjects affected / exposed   | 2 / 278 (0.72%)                              | 2 / 279 (0.72%)        |  |
| occurrences (all)   | 2  | 3                      |  |
| Breast cancer   | Additional description: Breast cancer        |                        |  |
| subjects affected / exposed   | 0 / 278 (0.00%)                              | 1 / 279 (0.36%)        |  |
| occurrences (all)   | 0  | 1                      |  |
| Colon adenoma   | Additional description: Colon adenoma        |                        |  |
| subjects affected / exposed   | 0 / 278 (0.00%)                              | 1 / 279 (0.36%)        |  |
| occurrences (all)   | 0  | 1                      |  |
| Histiocytosis   | Additional description: Histiocytosis        |                        |  |

|                                 |   |                 |  |
|---------------------------------|---|-----------------|--|
| subjects affected / exposed     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Oesophageal adenocarcinoma      | Additional description: Oesophageal adenocarcinoma      |                 |  |
| subjects affected / exposed     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences (all)               | 0   | 2               |  |
| Seborrhoeic keratosis           | Additional description: Seborrhoeic keratosis           |                 |  |
| subjects affected / exposed     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences (all)               | 0   | 1               |  |
| Skin cancer                     | Additional description: Skin cancer                     |                 |  |
| subjects affected / exposed     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Skin papilloma                  | Additional description: Skin papilloma                  |                 |  |
| subjects affected / exposed     | 2 / 278 (0.72%)   | 1 / 279 (0.36%) |  |
| occurrences (all)               | 2   | 1               |  |
| Squamous cell carcinoma of skin | Additional description: Squamous cell carcinoma of skin |                 |  |
| subjects affected / exposed     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences (all)               | 0   | 1               |  |
| Thyroid cancer                  | Additional description: Thyroid cancer                  |                 |  |
| subjects affected / exposed     | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences (all)               | 0   | 1               |  |
| Vascular disorders              |   |                 |  |
| Deep vein thrombosis            | Additional description: Deep vein thrombosis            |                 |  |
| subjects affected / exposed     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Haemorrhage                     | Additional description: Haemorrhage                     |                 |  |
| subjects affected / exposed     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Hot flush                       | Additional description: Hot flush                       |                 |  |
| subjects affected / exposed     | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Hypertension                    | Additional description: Hypertension                    |                 |  |
| subjects affected / exposed     | 4 / 278 (1.44%)   | 2 / 279 (0.72%) |  |
| occurrences (all)               | 4   | 3               |  |
| Hypotension                     | Additional description: Hypotension                     |                 |  |
| subjects affected / exposed     | 2 / 278 (0.72%)   | 0 / 279 (0.00%) |  |
| occurrences (all)               | 2   | 0               |  |

|  |  |                      |
|--|--|----------------------|
| Labile blood pressure<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Labile blood pressure    |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
| Peripheral ischaemia<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Peripheral ischaemia     |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Phlebitis                |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
| Post thrombotic syndrome<br>subjects affected / exposed<br>occurrences (all) | Additional description: Post thrombotic syndrome |                      |
|  | 0 / 278 (0.00%)<br>0                             | 1 / 279 (0.36%)<br>3 |
| Thrombosis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Thrombosis               |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
| Thrombophlebitis<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Thrombophlebitis         |                      |
|  | 0 / 278 (0.00%)<br>0                             | 1 / 279 (0.36%)<br>1 |
| Varicose vein<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Varicose vein            |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
| Venous thrombosis limb<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Venous thrombosis limb   |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
| Surgical and medical procedures  |  |                      |
|  | Additional description: Catheter management      |                      |
|  | 1 / 278 (0.36%)<br>1                             | 0 / 279 (0.00%)<br>0 |
|  | Additional description: Cervical conisation      |                      |
|  | 0 / 278 (0.00%)<br>0                             | 1 / 279 (0.36%)<br>1 |
| Haemorrhoid operation<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Haemorrhoid operation    |                      |
|  | 0 / 278 (0.00%)<br>0                             | 1 / 279 (0.36%)<br>1 |
| Hysterectomy   | Additional description: Hysterectomy             |                      |
|  |  |                      |



|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                          | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Immunoglobulin therapy                               | Additional description: Immunoglobulin therapy |                 |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)                                    | 1  | 1               |  |
| Papilloma excision                                   | Additional description: Papilloma excision     |                 |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Shoulder operation                                   | Additional description: Shoulder operation     |                 |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Skin neoplasm excision                               | Additional description: Skin neoplasm excision |                 |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| General disorders and administration site conditions |  |                 |  |
| Asthenia   | Additional description: Asthenia               |                 |  |
| subjects affected / exposed                          | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Chest pain   | Additional description: Chest pain             |                 |  |
| subjects affected / exposed                          | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Chills   | Additional description: Chills                 |                 |  |
| subjects affected / exposed                          | 4 / 278 (1.44%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)                                    | 4  | 1               |  |
| Fatigue  | Additional description: Fatigue                |                 |  |
| subjects affected / exposed                          | 6 / 278 (2.16%)                                | 8 / 279 (2.87%) |  |
| occurrences (all)                                    | 8  | 16              |  |
| Generalised oedema                                   | Additional description: Generalised oedema     |                 |  |
| subjects affected / exposed                          | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Inflammation   | Additional description: Inflammation           |                 |  |
| subjects affected / exposed                          | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Influenza like illness                               | Additional description: Influenza like illness |                 |  |

|                             |   |                   |  |
|-----------------------------|---|-------------------|--|
| subjects affected / exposed | 2 / 278 (0.72%)                                   | 3 / 279 (1.08%)   |  |
| occurrences (all)           | 2   | 5                 |  |
| Mucosal inflammation        | Additional description: Mucosal inflammation      |                   |  |
| subjects affected / exposed | 3 / 278 (1.08%)                                   | 2 / 279 (0.72%)   |  |
| occurrences (all)           | 3   | 2                 |  |
| Oedema                      | Additional description: Oedema                    |                   |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%)   |  |
| occurrences (all)           | 1   | 0                 |  |
| Pain                        | Additional description: Pain                      |                   |  |
| subjects affected / exposed | 2 / 278 (0.72%)                                   | 0 / 279 (0.00%)   |  |
| occurrences (all)           | 2   | 0                 |  |
| Peripheral swelling         | Additional description: Peripheral swelling       |                   |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Pyrexia                     | Additional description: Pyrexia                   |                   |  |
| subjects affected / exposed | 38 / 278 (13.67%)                                 | 42 / 279 (15.05%) |  |
| occurrences (all)           | 45  | 57                |  |
| Ulcer                       | Additional description: Ulcer                     |                   |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Immune system disorders     |   |                   |  |
| Anaphylactic reaction       | Additional description: Anaphylactic reaction     |                   |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Cytokine release syndrome   | Additional description: Cytokine release syndrome |                   |  |
| subjects affected / exposed | 3 / 278 (1.08%)                                   | 1 / 279 (0.36%)   |  |
| occurrences (all)           | 3   | 1                 |  |
| Drug hypersensitivity       | Additional description: Drug hypersensitivity     |                   |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%)   |  |
| occurrences (all)           | 1   | 1                 |  |
| Hypersensitivity            | Additional description: Hypersensitivity          |                   |  |
| subjects affected / exposed | 17 / 278 (6.12%)                                  | 10 / 279 (3.58%)  |  |
| occurrences (all)           | 19  | 10                |  |
| Hypogammaglobulinaemia      | Additional description: Hypogammaglobulinaemia    |                   |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%)   |  |
| occurrences (all)           | 4   | 0                 |  |

|   |   |                      |  |
|---|---|----------------------|--|
| Type IV hypersensitivity reaction<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Type IV hypersensitivity reaction     |                      |  |
|   | 0 / 278 (0.00%)<br>0  | 1 / 279 (0.36%)<br>1 |  |
| Reproductive system and breast disorders  |   |                      |  |
| Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Benign prostatic hyperplasia          |                      |  |
|   | 1 / 278 (0.36%)<br>1  | 0 / 279 (0.00%)<br>0 |  |
| Erectile dysfunction<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Erectile dysfunction                  |                      |  |
|   | 1 / 278 (0.36%)<br>7  | 0 / 279 (0.00%)<br>0 |  |
| Prostatitis<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Prostatitis                           |                      |  |
|   | 1 / 278 (0.36%)<br>1  | 1 / 279 (0.36%)<br>1 |  |
| Testicular pain<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Testicular pain                       |                      |  |
|   | 1 / 278 (0.36%)<br>1  | 0 / 279 (0.00%)<br>0 |  |
| Vaginal discharge<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Vaginal discharge                     |                      |  |
|   | 0 / 278 (0.00%)<br>0  | 1 / 279 (0.36%)<br>1 |  |
| Vulvovaginal dryness<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Vulvovaginal dryness                  |                      |  |
|   | 0 / 278 (0.00%)<br>0  | 1 / 279 (0.36%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders   |   |                      |  |
| Allergic bronchitis<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Allergic bronchitis                   |                      |  |
|   | 1 / 278 (0.36%)<br>1  | 0 / 279 (0.00%)<br>0 |  |
| Bronchitis chronic<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Bronchitis chronic                    |                      |  |
|   | 2 / 278 (0.72%)<br>2  | 1 / 279 (0.36%)<br>1 |  |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)                          | Additional description: Bronchospasm                          |                      |  |
|   | 0 / 278 (0.00%)<br>0  | 1 / 279 (0.36%)<br>1 |  |
| Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences (all) | Additional description: Chronic obstructive pulmonary disease |                      |  |
|   | 1 / 278 (0.36%)<br>1  | 1 / 279 (0.36%)<br>2 |  |

|                             |   |                  |
|-----------------------------|---|------------------|
| Chylothorax                 | Additional description: Chylothorax         |                  |
| subjects affected / exposed | 1 / 278 (0.36%)                             | 0 / 279 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Cough                       | Additional description: Cough               |                  |
| subjects affected / exposed | 10 / 278 (3.60%)                            | 18 / 279 (6.45%) |
| occurrences (all)           | 11  | 25               |
| Cough decreased             | Additional description: Cough decreased     |                  |
| subjects affected / exposed | 0 / 278 (0.00%)                             | 1 / 279 (0.36%)  |
| occurrences (all)           | 0   | 1                |
| Dyspnoea                    | Additional description: Dyspnoea            |                  |
| subjects affected / exposed | 3 / 278 (1.08%)                             | 4 / 279 (1.43%)  |
| occurrences (all)           | 11  | 7                |
| Dyspnoea exertional         | Additional description: Dyspnoea exertional |                  |
| subjects affected / exposed | 1 / 278 (0.36%)                             | 0 / 279 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Epistaxis                   | Additional description: Epistaxis           |                  |
| subjects affected / exposed | 1 / 278 (0.36%)                             | 0 / 279 (0.00%)  |
| occurrences (all)           | 2   | 0                |
| Oropharyngeal pain          | Additional description: Oropharyngeal pain  |                  |
| subjects affected / exposed | 2 / 278 (0.72%)                             | 1 / 279 (0.36%)  |
| occurrences (all)           | 2   | 1                |
| Pleural effusion            | Additional description: Pleural effusion    |                  |
| subjects affected / exposed | 0 / 278 (0.00%)                             | 2 / 279 (0.72%)  |
| occurrences (all)           | 0   | 2                |
| Productive cough            | Additional description: Productive cough    |                  |
| subjects affected / exposed | 0 / 278 (0.00%)                             | 1 / 279 (0.36%)  |
| occurrences (all)           | 0   | 1                |
| Rhinitis allergic           | Additional description: Rhinitis allergic   |                  |
| subjects affected / exposed | 0 / 278 (0.00%)                             | 1 / 279 (0.36%)  |
| occurrences (all)           | 0   | 1                |
| Rhinitis atrophic           | Additional description: Rhinitis atrophic   |                  |
| subjects affected / exposed | 1 / 278 (0.36%)                             | 0 / 279 (0.00%)  |
| occurrences (all)           | 1   | 0                |
| Rhinorrhoea                 | Additional description: Rhinorrhoea         |                  |
| subjects affected / exposed | 0 / 278 (0.00%)                             | 2 / 279 (0.72%)  |
| occurrences (all)           | 0   | 3                |

|                                       |   |                 |  |
|---------------------------------------|---|-----------------|--|
| Psychiatric disorders                 |   |                 |  |
| Depression                            | Additional description: Depression                            |                 |  |
| subjects affected / exposed           | 4 / 278 (1.44%)   | 2 / 279 (0.72%) |  |
| occurrences (all)                     | 6   | 2               |  |
| Insomnia                              | Additional description: Insomnia                              |                 |  |
| subjects affected / exposed           | 1 / 278 (0.36%)   | 1 / 279 (0.36%) |  |
| occurrences (all)                     | 4   | 2               |  |
| Schizophrenia                         | Additional description: Schizophrenia                         |                 |  |
| subjects affected / exposed           | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Investigations                        |   |                 |  |
| Alanine aminotransferase              | Additional description: Alanine aminotransferase              |                 |  |
| subjects affected / exposed           | 0 / 278 (0.00%)   | 3 / 279 (1.08%) |  |
| occurrences (all)                     | 0   | 5               |  |
| Alanine aminotransferase increased    | Additional description: Alanine aminotransferase increased    |                 |  |
| subjects affected / exposed           | 0 / 278 (0.00%)   | 3 / 279 (1.08%) |  |
| occurrences (all)                     | 0   | 4               |  |
| Aspartate aminotransferase            | Additional description: Aspartate aminotransferase            |                 |  |
| subjects affected / exposed           | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences (all)                     | 0   | 4               |  |
| Aspartate aminotransferase increased  | Additional description: Aspartate aminotransferase increased  |                 |  |
| subjects affected / exposed           | 0 / 278 (0.00%)   | 2 / 279 (0.72%) |  |
| occurrences (all)                     | 0   | 2               |  |
| Blood creatinine increased            | Additional description: Blood creatinine increased            |                 |  |
| subjects affected / exposed           | 1 / 278 (0.36%)   | 1 / 279 (0.36%) |  |
| occurrences (all)                     | 1   | 1               |  |
| Blood creatinine                      | Additional description: Blood creatinine                      |                 |  |
| subjects affected / exposed           | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Blood bilirubin                       | Additional description: Blood bilirubin                       |                 |  |
| subjects affected / exposed           | 1 / 278 (0.36%)   | 0 / 279 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Blood alkaline phosphatase increased  | Additional description: Blood alkaline phosphatase increased  |                 |  |
| subjects affected / exposed           | 0 / 278 (0.00%)   | 1 / 279 (0.36%) |  |
| occurrences (all)                     | 0   | 1               |  |
| Blood lactate dehydrogenase increased | Additional description: Blood lactate dehydrogenase increased |                 |  |

|                                     |   |                  |  |
|-------------------------------------|---|------------------|--|
| subjects affected / exposed         | 0 / 278 (0.00%)   | 1 / 279 (0.36%)  |  |
| occurrences (all)                   | 0   | 1                |  |
| Body temperature increased          | Additional description: Body temperature increased          |                  |  |
| subjects affected / exposed         | 1 / 278 (0.36%)   | 0 / 279 (0.00%)  |  |
| occurrences (all)                   | 1   | 0                |  |
| Blood potassium decreased           | Additional description: Blood potassium decreased           |                  |  |
| subjects affected / exposed         | 0 / 278 (0.00%)   | 1 / 279 (0.36%)  |  |
| occurrences (all)                   | 0   | 2                |  |
| C-reactive protein increased        | Additional description: C-reactive protein increased        |                  |  |
| subjects affected / exposed         | 2 / 278 (0.72%)   | 0 / 279 (0.00%)  |  |
| occurrences (all)                   | 2   | 0                |  |
| CD4 lymphocytes                     | Additional description: CD4 lymphocytes                     |                  |  |
| subjects affected / exposed         | 1 / 278 (0.36%)   | 0 / 279 (0.00%)  |  |
| occurrences (all)                   | 2   | 0                |  |
| CD4 lymphocytes decreased           | Additional description: CD4 lymphocytes decreased           |                  |  |
| subjects affected / exposed         | 1 / 278 (0.36%)   | 1 / 279 (0.36%)  |  |
| occurrences (all)                   | 1   | 9                |  |
| Gamma-glutamyltransferase increased | Additional description: Gamma-glutamyltransferase increased |                  |  |
| subjects affected / exposed         | 0 / 278 (0.00%)   | 3 / 279 (1.08%)  |  |
| occurrences (all)                   | 0   | 4                |  |
| Gamma-glutamyltransferase           | Additional description: Gamma-glutamyltransferase           |                  |  |
| subjects affected / exposed         | 0 / 278 (0.00%)   | 2 / 279 (0.72%)  |  |
| occurrences (all)                   | 0   | 11               |  |
| Haemoglobin                         | Additional description: Haemoglobin                         |                  |  |
| subjects affected / exposed         | 9 / 278 (3.24%)   | 10 / 279 (3.58%) |  |
| occurrences (all)                   | 17  | 35               |  |
| Granulocytes abnormal               | Additional description: Granulocytes abnormal               |                  |  |
| subjects affected / exposed         | 0 / 278 (0.00%)   | 1 / 279 (0.36%)  |  |
| occurrences (all)                   | 0   | 5                |  |
| Haemoglobin decreased               | Additional description: Haemoglobin decreased               |                  |  |
| subjects affected / exposed         | 0 / 278 (0.00%)   | 2 / 279 (0.72%)  |  |
| occurrences (all)                   | 0   | 3                |  |
| Hepatitis B antibody positive       | Additional description: Hepatitis B antibody positive       |                  |  |
| subjects affected / exposed         | 0 / 278 (0.00%)   | 1 / 279 (0.36%)  |  |
| occurrences (all)                   | 0   | 1                |  |

|  |  |                         |
|--|--|-------------------------|
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Hepatic enzyme increased       |                         |
|  | 1 / 278 (0.36%)<br>1                                   | 1 / 279 (0.36%)<br>2    |
| Immunoglobulins decreased<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Immunoglobulins decreased      |                         |
|  | 1 / 278 (0.36%)<br>3                                   | 1 / 279 (0.36%)<br>1    |
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all) | Additional description: Intraocular pressure increased |                         |
|  | 1 / 278 (0.36%)<br>1                                   | 0 / 279 (0.00%)<br>0    |
| Lipase<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Lipase                         |                         |
|  | 0 / 278 (0.00%)<br>0                                   | 1 / 279 (0.36%)<br>1    |
| Neutrophil count<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Neutrophil count               |                         |
|  | 20 / 278 (7.19%)<br>41                                 | 33 / 279 (11.83%)<br>89 |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Neutrophil count decreased     |                         |
|  | 1 / 278 (0.36%)<br>2                                   | 3 / 279 (1.08%)<br>3    |
| Platelet count<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Platelet count                 |                         |
|  | 0 / 278 (0.00%)<br>0                                   | 2 / 279 (0.72%)<br>2    |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Platelet count decreased       |                         |
|  | 1 / 278 (0.36%)<br>2                                   | 0 / 279 (0.00%)<br>0    |
| Prothrombin time shortened<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Prothrombin time shortened     |                         |
|  | 0 / 278 (0.00%)<br>0                                   | 1 / 279 (0.36%)<br>1    |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Transaminases increased        |                         |
|  | 0 / 278 (0.00%)<br>0                                   | 1 / 279 (0.36%)<br>1    |
| White blood cell count<br>subjects affected / exposed<br>occurrences (all)         | Additional description: White blood cell count         |                         |
|  | 15 / 278 (5.40%)<br>38                                 | 26 / 279 (9.32%)<br>92  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Weight decreased               |                         |
|  | 1 / 278 (0.36%)<br>1                                   | 0 / 279 (0.00%)<br>0    |

|  |   |                 |  |
|--|---|-----------------|--|
| Injury, poisoning and procedural complications |   |                 |  |
| Arterial injury                                | Additional description: Arterial injury           |                 |  |
| subjects affected / exposed                    | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 0   | 8               |  |
| Foot fracture                                  | Additional description: Foot fracture             |                 |  |
| subjects affected / exposed                    | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences (all)                              | 1   | 0               |  |
| Infusion related reaction                      | Additional description: Infusion related reaction |                 |  |
| subjects affected / exposed                    | 2 / 278 (0.72%)                                   | 3 / 279 (1.08%) |  |
| occurrences (all)                              | 2   | 3               |  |
| Meniscus injury                                | Additional description: Meniscus injury           |                 |  |
| subjects affected / exposed                    | 2 / 278 (0.72%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 2   | 1               |  |
| Postoperative fever                            | Additional description: Postoperative fever       |                 |  |
| subjects affected / exposed                    | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 0   | 1               |  |
| Skull fracture                                 | Additional description: Skull fracture            |                 |  |
| subjects affected / exposed                    | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 0   | 1               |  |
| Wound  | Additional description: Wound                     |                 |  |
| subjects affected / exposed                    | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 1   | 1               |  |
| Cardiac disorders                              |   |                 |  |
| Angina pectoris                                | Additional description: Angina pectoris           |                 |  |
| subjects affected / exposed                    | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences (all)                              | 1   | 0               |  |
| Arrhythmia                                     | Additional description: Arrhythmia                |                 |  |
| subjects affected / exposed                    | 3 / 278 (1.08%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 3   | 1               |  |
| Atrial fibrillation                            | Additional description: Atrial fibrillation       |                 |  |
| subjects affected / exposed                    | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 0   | 1               |  |
| Cardiac failure                                | Additional description: Cardiac failure           |                 |  |
| subjects affected / exposed                    | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)                              | 0   | 1               |  |
| Myocardial ischaemia                           | Additional description: Myocardial ischaemia      |                 |  |



|                                  |  |                 |  |
|----------------------------------|--|-----------------|--|
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Tachycardia                      | Additional description: Tachycardia                      |                 |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences (all)                | 2  | 0               |  |
| Tachyarrhythmia                  | Additional description: Tachyarrhythmia                  |                 |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences (all)                | 0  | 1               |  |
| Nervous system disorders         |  |                 |  |
| Carotid artery stenosis          | Additional description: Carotid artery stenosis          |                 |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences (all)                | 0  | 1               |  |
| Carpal tunnel syndrome           | Additional description: Carpal tunnel syndrome           |                 |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 2 / 279 (0.72%) |  |
| occurrences (all)                | 0  | 4               |  |
| Cervicogenic headache            | Additional description: Cervicogenic headache            |                 |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences (all)                | 0  | 1               |  |
| Depressed level of consciousness | Additional description: Depressed level of consciousness |                 |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Dizziness                        | Additional description: Dizziness                        |                 |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 2 / 279 (0.72%) |  |
| occurrences (all)                | 0  | 2               |  |
| Dystonia                         | Additional description: Dystonia                         |                 |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Headache                         | Additional description: Headache                         |                 |  |
| subjects affected / exposed      | 3 / 278 (1.08%)  | 0 / 279 (0.00%) |  |
| occurrences (all)                | 3  | 0               |  |
| Hypoaesthesia                    | Additional description: Hypoaesthesia                    |                 |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Monoparesis                      | Additional description: Monoparesis                      |                 |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |  |
| occurrences (all)                | 0  | 1               |  |

|   |   |                      |
|---|---|----------------------|
| Migraine with aura<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Migraine with aura            |                      |
|   | 1 / 278 (0.36%)<br>1                                  | 0 / 279 (0.00%)<br>0 |
| Memory impairment<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Memory impairment             |                      |
|   | 1 / 278 (0.36%)<br>1                                  | 0 / 279 (0.00%)<br>0 |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Neuralgia                     |                      |
|   | 0 / 278 (0.00%)<br>0                                  | 1 / 279 (0.36%)<br>1 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Paraesthesia                  |                      |
|   | 0 / 278 (0.00%)<br>0                                  | 2 / 279 (0.72%)<br>2 |
| Paresis cranial nerve<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Paresis cranial nerve         |                      |
|   | 1 / 278 (0.36%)<br>1                                  | 0 / 279 (0.00%)<br>0 |
| Parkinson's disease<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Parkinson's disease           |                      |
|   | 0 / 278 (0.00%)<br>0                                  | 1 / 279 (0.36%)<br>1 |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | Additional description: Peripheral sensory neuropathy |                      |
|   | 1 / 278 (0.36%)<br>1                                  | 0 / 279 (0.00%)<br>0 |
| Polyneuropathy<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Polyneuropathy                |                      |
|   | 3 / 278 (1.08%)<br>10                                 | 2 / 279 (0.72%)<br>2 |
| Post herpetic neuralgia<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Post herpetic neuralgia       |                      |
|   | 0 / 278 (0.00%)<br>0                                  | 2 / 279 (0.72%)<br>5 |
| Restless legs syndrome<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Restless legs syndrome        |                      |
|   | 1 / 278 (0.36%)<br>1                                  | 0 / 279 (0.00%)<br>0 |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Syncope                       |                      |
|   | 3 / 278 (1.08%)<br>3                                  | 0 / 279 (0.00%)<br>0 |
| Transient ischaemic attack<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Transient ischaemic attack    |                      |
|   | 0 / 278 (0.00%)<br>0                                  | 1 / 279 (0.36%)<br>1 |

|                                      |  |                    |  |
|--------------------------------------|--|--------------------|--|
| Blood and lymphatic system disorders |  |                    |  |
| Anaemia vitamin B12 deficiency       | Additional description: Anaemia vitamin B12 deficiency |                    |  |
| subjects affected / exposed          | 1 / 278 (0.36%)  | 0 / 279 (0.00%)    |  |
| occurrences (all)                    | 1  | 0                  |  |
| Anaemia folate deficiency            | Additional description: Anaemia folate deficiency      |                    |  |
| subjects affected / exposed          | 1 / 278 (0.36%)  | 0 / 279 (0.00%)    |  |
| occurrences (all)                    | 1  | 0                  |  |
| Anaemia                              | Additional description: Anaemia                        |                    |  |
| subjects affected / exposed          | 18 / 278 (6.47%)                                       | 26 / 279 (9.32%)   |  |
| occurrences (all)                    | 30   | 39                 |  |
| Autoimmune haemolytic anaemia        | Additional description: Autoimmune haemolytic anaemia  |                    |  |
| subjects affected / exposed          | 1 / 278 (0.36%)  | 0 / 279 (0.00%)    |  |
| occurrences (all)                    | 1  | 0                  |  |
| Febrile neutropenia                  | Additional description: Febrile neutropenia            |                    |  |
| subjects affected / exposed          | 4 / 278 (1.44%)  | 4 / 279 (1.43%)    |  |
| occurrences (all)                    | 6  | 4                  |  |
| Granulocytopenia                     | Additional description: Granulocytopenia               |                    |  |
| subjects affected / exposed          | 3 / 278 (1.08%)  | 3 / 279 (1.08%)    |  |
| occurrences (all)                    | 4  | 3                  |  |
| Haemolytic anaemia                   | Additional description: Haemolytic anaemia             |                    |  |
| subjects affected / exposed          | 1 / 278 (0.36%)  | 0 / 279 (0.00%)    |  |
| occurrences (all)                    | 1  | 0                  |  |
| Haemolysis                           | Additional description: Haemolysis                     |                    |  |
| subjects affected / exposed          | 1 / 278 (0.36%)  | 1 / 279 (0.36%)    |  |
| occurrences (all)                    | 2  | 1                  |  |
| Leukopenia                           | Additional description: Leukopenia                     |                    |  |
| subjects affected / exposed          | 127 / 278 (45.68%)                                     | 208 / 279 (74.55%) |  |
| occurrences (all)                    | 321  | 818                |  |
| Neutropenia                          | Additional description: Neutropenia                    |                    |  |
| subjects affected / exposed          | 153 / 278 (55.04%)                                     | 216 / 279 (77.42%) |  |
| occurrences (all)                    | 369  | 802                |  |
| Pancytopenia                         | Additional description: Pancytopenia                   |                    |  |
| subjects affected / exposed          | 0 / 278 (0.00%)  | 2 / 279 (0.72%)    |  |
| occurrences (all)                    | 0  | 3                  |  |
| Platelet disorder                    | Additional description: Platelet disorder              |                    |  |

|                                  |  |                   |  |
|----------------------------------|--|-------------------|--|
| subjects affected / exposed      | 5 / 278 (1.80%)  | 8 / 279 (2.87%)   |  |
| occurrences (all)                | 6  | 22                |  |
| Thrombocytopenia                 | Additional description: Thrombocytopenia                 |                   |  |
| subjects affected / exposed      | 45 / 278 (16.19%)  | 61 / 279 (21.86%) |  |
| occurrences (all)                | 86   | 138               |  |
| Ear and labyrinth disorders      |  |                   |  |
| Deafness                         | Additional description: Deafness                         |                   |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%)   |  |
| occurrences (all)                | 1  | 0                 |  |
| Hearing impaired                 | Additional description: Hearing impaired                 |                   |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%)   |  |
| occurrences (all)                | 1  | 0                 |  |
| Tinnitus                         | Additional description: Tinnitus                         |                   |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 1 / 279 (0.36%)   |  |
| occurrences (all)                | 1  | 1                 |  |
| Vestibular disorder              | Additional description: Vestibular disorder              |                   |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%)   |  |
| occurrences (all)                | 0  | 2                 |  |
| Vertigo                          | Additional description: Vertigo                          |                   |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%)   |  |
| occurrences (all)                | 1  | 0                 |  |
| Eye disorders                    |  |                   |  |
| Age-related macular degeneration | Additional description: Age-related macular degeneration |                   |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%)   |  |
| occurrences (all)                | 0  | 1                 |  |
| Glaucoma                         | Additional description: Glaucoma                         |                   |  |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 0 / 279 (0.00%)   |  |
| occurrences (all)                | 2  | 0                 |  |
| Lacrimation increased            | Additional description: Lacrimation increased            |                   |  |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%)   |  |
| occurrences (all)                | 0  | 1                 |  |
| Visual impairment                | Additional description: Visual impairment                |                   |  |
| subjects affected / exposed      | 2 / 278 (0.72%)  | 0 / 279 (0.00%)   |  |
| occurrences (all)                | 3  | 0                 |  |
| Gastrointestinal disorders       |  |                   |  |

|  |  |                      |  |
|--|--|----------------------|--|
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | Additional description: Abdominal distension<br>1 / 278 (0.36%)<br>1 | 0 / 279 (0.00%)<br>0 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | Additional description: Abdominal pain upper<br>2 / 278 (0.72%)<br>2 | 0 / 279 (0.00%)<br>0 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Abdominal pain<br>1 / 278 (0.36%)<br>1       | 3 / 279 (1.08%)<br>3 |  |
| Anal fissure<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Anal fissure<br>1 / 278 (0.36%)<br>1         | 0 / 279 (0.00%)<br>0 |  |
| Anal prolapse<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Anal prolapse<br>1 / 278 (0.36%)<br>2        | 0 / 279 (0.00%)<br>0 |  |
| Anal ulcer<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Anal ulcer<br>0 / 278 (0.00%)<br>0           | 1 / 279 (0.36%)<br>1 |  |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Aphthous stomatitis<br>0 / 278 (0.00%)<br>0  | 1 / 279 (0.36%)<br>1 |  |
| Chronic gastritis<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Chronic gastritis<br>1 / 278 (0.36%)<br>1    | 0 / 279 (0.00%)<br>0 |  |
| Colitis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Colitis<br>0 / 278 (0.00%)<br>0              | 1 / 279 (0.36%)<br>1 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Constipation<br>1 / 278 (0.36%)<br>1         | 2 / 279 (0.72%)<br>2 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Diarrhoea<br>2 / 278 (0.72%)<br>2            | 4 / 279 (1.43%)<br>6 |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Dyspepsia<br>0 / 278 (0.00%)<br>0            | 1 / 279 (0.36%)<br>1 |  |

|                                  |  |                 |
|----------------------------------|--|-----------------|
| Enteritis                        | Additional description: Enteritis                        |                 |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 2 / 279 (0.72%) |
| occurrences (all)                | 1  | 2               |
| Enterocolitis                    | Additional description: Enterocolitis                    |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 2 / 279 (0.72%) |
| occurrences (all)                | 0  | 2               |
| Gastric ulcer                    | Additional description: Gastric ulcer                    |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                | 0  | 1               |
| Gastritis                        | Additional description: Gastritis                        |                 |
| subjects affected / exposed      | 3 / 278 (1.08%)  | 0 / 279 (0.00%) |
| occurrences (all)                | 5  | 0               |
| Gastrooesophageal reflux disease | Additional description: Gastrooesophageal reflux disease |                 |
| subjects affected / exposed      | 3 / 278 (1.08%)  | 0 / 279 (0.00%) |
| occurrences (all)                | 4  | 0               |
| Haemorrhoids                     | Additional description: Haemorrhoids                     |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                | 0  | 1               |
| Ileus                            | Additional description: Ileus                            |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                | 0  | 1               |
| Inguinal hernia                  | Additional description: Inguinal hernia                  |                 |
| subjects affected / exposed      | 1 / 278 (0.36%)  | 1 / 279 (0.36%) |
| occurrences (all)                | 1  | 1               |
| Nausea                           | Additional description: Nausea                           |                 |
| subjects affected / exposed      | 7 / 278 (2.52%)  | 5 / 279 (1.79%) |
| occurrences (all)                | 7  | 8               |
| Oral mucosal discolouration      | Additional description: Oral mucosal discolouration      |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                | 0  | 1               |
| Periodontal inflammation         | Additional description: Periodontal inflammation         |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                | 0  | 1               |
| Stomatitis                       | Additional description: Stomatitis                       |                 |
| subjects affected / exposed      | 0 / 278 (0.00%)  | 4 / 279 (1.43%) |
| occurrences (all)                | 0  | 4               |

|   |   |                 |
|---|---|-----------------|
| Toothache<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Toothache               |                 |
|   | 1 / 278 (0.36%)                                 | 0 / 279 (0.00%) |
|   | 1   | 0               |
| Tooth loss<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Tooth loss              |                 |
|   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |
|   | 0   | 1               |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Vomiting                |                 |
|   | 5 / 278 (1.80%)                                 | 4 / 279 (1.43%) |
|   | 5   | 6               |
| Hepatobiliary disorders   |   |                 |
|   | Additional description: Cholelithiasis          |                 |
|   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |
|   | 0   | 1               |
|   | Additional description: Hepatitis alcoholic     |                 |
|   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |
| Hepatitis alcoholic<br>subjects affected / exposed<br>occurrences (all)     | 0   | 2               |
|   | Additional description: Hyperbilirubinaemia     |                 |
|   | 1 / 278 (0.36%)                                 | 1 / 279 (0.36%) |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)     | 1   | 2               |
|   |   |                 |
|   |   |                 |
| Skin and subcutaneous tissue disorders                                      |   |                 |
|   | Additional description: Acne                    |                 |
|   | 1 / 278 (0.36%)                                 | 1 / 279 (0.36%) |
|   | 1   | 1               |
|   | Additional description: Actinic keratosis       |                 |
|   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |
|   | 0   | 1               |
|   | Additional description: Blister                 |                 |
|   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |
|   | 0   | 1               |
|   | Additional description: Dermatitis allergic     |                 |
|   | 1 / 278 (0.36%)                                 | 1 / 279 (0.36%) |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)     | 1   | 1               |
|   | Additional description: Dermatitis psoriasiform |                 |
|   | 0 / 278 (0.00%)                                 | 1 / 279 (0.36%) |
| Dermatitis psoriasiform<br>subjects affected / exposed<br>occurrences (all) | 0   | 1               |
|   | Additional description: Dry skin                |                 |
|   |   |                 |
| Dry skin  |   |                 |
|   |   |                 |

|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)           | 1   | 1               |  |
| Eczema                      | Additional description: Eczema                    |                 |  |
| subjects affected / exposed | 2 / 278 (0.72%)                                   | 2 / 279 (0.72%) |  |
| occurrences (all)           | 3   | 2               |  |
| Erythema                    | Additional description: Erythema                  |                 |  |
| subjects affected / exposed | 3 / 278 (1.08%)                                   | 5 / 279 (1.79%) |  |
| occurrences (all)           | 4   | 10              |  |
| Erythema nodosum            | Additional description: Erythema nodosum          |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)           | 0   | 1               |  |
| Erythema multiforme         | Additional description: Erythema multiforme       |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Hyperhidrosis               | Additional description: Hyperhidrosis             |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 4 / 279 (1.43%) |  |
| occurrences (all)           | 0   | 6               |  |
| Hyperkeratosis              | Additional description: Hyperkeratosis            |                 |  |
| subjects affected / exposed | 2 / 278 (0.72%)                                   | 0 / 279 (0.00%) |  |
| occurrences (all)           | 4   | 0               |  |
| Neurodermatitis             | Additional description: Neurodermatitis           |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 2 / 279 (0.72%) |  |
| occurrences (all)           | 0   | 11              |  |
| Petechiae                   | Additional description: Petechiae                 |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)           | 0   | 1               |  |
| Photosensitivity reaction   | Additional description: Photosensitivity reaction |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Pruritus                    | Additional description: Pruritus                  |                 |  |
| subjects affected / exposed | 11 / 278 (3.96%)                                  | 8 / 279 (2.87%) |  |
| occurrences (all)           | 16  | 12              |  |
| Psoriasis                   | Additional description: Psoriasis                 |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%) |  |
| occurrences (all)           | 1   | 1               |  |
| Rash                        | Additional description: Rash                      |                 |  |



|                             |   |                  |  |
|-----------------------------|---|------------------|--|
| subjects affected / exposed | 16 / 278 (5.76%)                              | 16 / 279 (5.73%) |  |
| occurrences (all)           | 30  | 18               |  |
| Rash generalised            | Additional description: Rash generalised      |                  |  |
| subjects affected / exposed | 1 / 278 (0.36%)                               | 0 / 279 (0.00%)  |  |
| occurrences (all)           | 1   | 0                |  |
| Rash maculo-papular         | Additional description: Rash maculo-papular   |                  |  |
| subjects affected / exposed | 0 / 278 (0.00%)                               | 2 / 279 (0.72%)  |  |
| occurrences (all)           | 0   | 6                |  |
| Rash pruritic               | Additional description: Rash pruritic         |                  |  |
| subjects affected / exposed | 0 / 278 (0.00%)                               | 1 / 279 (0.36%)  |  |
| occurrences (all)           | 0   | 1                |  |
| Rash papular                | Additional description: Rash papular          |                  |  |
| subjects affected / exposed | 0 / 278 (0.00%)                               | 1 / 279 (0.36%)  |  |
| occurrences (all)           | 0   | 1                |  |
| Skin exfoliation            | Additional description: Skin exfoliation      |                  |  |
| subjects affected / exposed | 5 / 278 (1.80%)                               | 0 / 279 (0.00%)  |  |
| occurrences (all)           | 7   | 0                |  |
| Skin lesion                 | Additional description: Skin lesion           |                  |  |
| subjects affected / exposed | 2 / 278 (0.72%)                               | 0 / 279 (0.00%)  |  |
| occurrences (all)           | 2   | 0                |  |
| Skin texture abnormal       | Additional description: Skin texture abnormal |                  |  |
| subjects affected / exposed | 1 / 278 (0.36%)                               | 0 / 279 (0.00%)  |  |
| occurrences (all)           | 1   | 0                |  |
| Skin ulcer                  | Additional description: Skin ulcer            |                  |  |
| subjects affected / exposed | 0 / 278 (0.00%)                               | 2 / 279 (0.72%)  |  |
| occurrences (all)           | 0   | 4                |  |
| Urticaria                   | Additional description: Urticaria             |                  |  |
| subjects affected / exposed | 5 / 278 (1.80%)                               | 1 / 279 (0.36%)  |  |
| occurrences (all)           | 7   | 1                |  |
| Renal and urinary disorders |   |                  |  |
| Cystitis noninfective       | Additional description: Cystitis noninfective |                  |  |
| subjects affected / exposed | 0 / 278 (0.00%)                               | 1 / 279 (0.36%)  |  |
| occurrences (all)           | 0   | 1                |  |
| Dysuria                     | Additional description: Dysuria               |                  |  |
| subjects affected / exposed | 1 / 278 (0.36%)                               | 0 / 279 (0.00%)  |  |
| occurrences (all)           | 1   | 0                |  |

|   |  |                 |
|---|--|-----------------|
| Pollakiuria                                     | Additional description: Pollakiuria                    |                 |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |
| occurrences (all)                               | 1  | 0               |
| Renal colic                                     | Additional description: Renal colic                    |                 |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                               | 0  | 1               |
| Renal failure                                   | Additional description: Renal failure                  |                 |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                               | 0  | 1               |
| Stress urinary incontinence                     | Additional description: Stress urinary incontinence    |                 |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |
| occurrences (all)                               | 1  | 0               |
| Endocrine disorders                             |  |                 |
| Autoimmune thyroiditis                          | Additional description: Autoimmune thyroiditis         |                 |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |
| occurrences (all)                               | 1  | 0               |
| Hyperthyroidism                                 | Additional description: Hyperthyroidism                |                 |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 2 / 279 (0.72%) |
| occurrences (all)                               | 0  | 2               |
| Musculoskeletal and connective tissue disorders |  |                 |
| Arthralgia                                      | Additional description: Arthralgia                     |                 |
| subjects affected / exposed                     | 3 / 278 (1.08%)  | 4 / 279 (1.43%) |
| occurrences (all)                               | 6  | 9               |
| Arthritis                                       | Additional description: Arthritis                      |                 |
| subjects affected / exposed                     | 0 / 278 (0.00%)  | 1 / 279 (0.36%) |
| occurrences (all)                               | 0  | 1               |
| Arthrofibrosis                                  | Additional description: Arthrofibrosis                 |                 |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 0 / 279 (0.00%) |
| occurrences (all)                               | 1  | 0               |
| Back pain                                       | Additional description: Back pain                      |                 |
| subjects affected / exposed                     | 3 / 278 (1.08%)  | 4 / 279 (1.43%) |
| occurrences (all)                               | 6  | 6               |
| Intervertebral disc protrusion                  | Additional description: Intervertebral disc protrusion |                 |
| subjects affected / exposed                     | 1 / 278 (0.36%)  | 1 / 279 (0.36%) |
| occurrences (all)                               | 1  | 1               |
| Musculoskeletal pain                            | Additional description: Musculoskeletal pain           |                 |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 3 / 278 (1.08%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)           | 5  | 0               |  |
| Muscle spasms               | Additional description: Muscle spasms          |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 1  | 1               |  |
| Neck pain                   | Additional description: Neck pain              |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 0  | 1               |  |
| Osteoarthritis              | Additional description: Osteoarthritis         |                 |  |
| subjects affected / exposed | 3 / 278 (1.08%)                                | 2 / 279 (0.72%) |  |
| occurrences (all)           | 5  | 6               |  |
| Osteopenia                  | Additional description: Osteopenia             |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Osteoporosis                | Additional description: Osteoporosis           |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                | 2 / 279 (0.72%) |  |
| occurrences (all)           | 0  | 2               |  |
| Pain in extremity           | Additional description: Pain in extremity      |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 1  | 1               |  |
| Periarthritis               | Additional description: Periarthritis          |                 |  |
| subjects affected / exposed | 2 / 278 (0.72%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)           | 3  | 0               |  |
| Polyarthritis               | Additional description: Polyarthritis          |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)           | 2  | 0               |  |
| Polymyalgia rheumatica      | Additional description: Polymyalgia rheumatica |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)           | 3  | 0               |  |
| Rheumatoid arthritis        | Additional description: Rheumatoid arthritis   |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 0 / 279 (0.00%) |  |
| occurrences (all)           | 6  | 0               |  |
| Scoliosis                   | Additional description: Scoliosis              |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 0  | 1               |  |
| Rotator cuff syndrome       | Additional description: Rotator cuff syndrome  |                 |  |

|                               |   |                   |  |
|-------------------------------|---|-------------------|--|
| subjects affected / exposed   | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%)   |  |
| occurrences (all)             | 0   | 2                 |  |
| Seronegative arthritis        | Additional description: Seronegative arthritis        |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%)   |  |
| occurrences (all)             | 3   | 0                 |  |
| Spinal osteoarthritis         | Additional description: Spinal osteoarthritis         |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%)   |  |
| occurrences (all)             | 1   | 0                 |  |
| Infections and infestations   |   |                   |  |
| Abscess                       | Additional description: Abscess                       |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%)   |  |
| occurrences (all)             | 1   | 0                 |  |
| Abscess jaw                   | Additional description: Abscess jaw                   |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%)   |  |
| occurrences (all)             | 1   | 0                 |  |
| Acute tonsillitis             | Additional description: Acute tonsillitis             |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 1 / 279 (0.36%)   |  |
| occurrences (all)             | 1   | 1                 |  |
| Aspergillus infection         | Additional description: Aspergillus infection         |                   |  |
| subjects affected / exposed   | 0 / 278 (0.00%)                                       | 1 / 279 (0.36%)   |  |
| occurrences (all)             | 0   | 1                 |  |
| Bacteraemia                   | Additional description: Bacteraemia                   |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 0 / 279 (0.00%)   |  |
| occurrences (all)             | 1   | 0                 |  |
| Bronchitis                    | Additional description: Bronchitis                    |                   |  |
| subjects affected / exposed   | 31 / 278 (11.15%)                                     | 30 / 279 (10.75%) |  |
| occurrences (all)             | 44  | 47                |  |
| Bronchopneumonia              | Additional description: Bronchopneumonia              |                   |  |
| subjects affected / exposed   | 2 / 278 (0.72%)                                       | 3 / 279 (1.08%)   |  |
| occurrences (all)             | 2   | 5                 |  |
| Campylobacter gastroenteritis | Additional description: Campylobacter gastroenteritis |                   |  |
| subjects affected / exposed   | 1 / 278 (0.36%)                                       | 1 / 279 (0.36%)   |  |
| occurrences (all)             | 1   | 1                 |  |
| Candida infection             | Additional description: Candida infection             |                   |  |
| subjects affected / exposed   | 2 / 278 (0.72%)                                       | 1 / 279 (0.36%)   |  |
| occurrences (all)             | 2   | 2                 |  |

|   |   |                 |
|---|---|-----------------|
| Chronic sinusitis<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Chronic sinusitis         |                 |
|   | 0 / 278 (0.00%)                                   | 2 / 279 (0.72%) |
|   | 0   | 2               |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Conjunctivitis            |                 |
|   | 3 / 278 (1.08%)                                   | 2 / 279 (0.72%) |
|   | 3   | 2               |
| Cytomegalovirus infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Cytomegalovirus infection |                 |
|   | 0 / 278 (0.00%)                                   | 2 / 279 (0.72%) |
|   | 0   | 2               |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Cystitis                  |                 |
|   | 2 / 278 (0.72%)                                   | 3 / 279 (1.08%) |
|   | 2   | 5               |
| Diverticulitis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Diverticulitis            |                 |
|   | 0 / 278 (0.00%)                                   | 1 / 279 (0.36%) |
|   | 0   | 1               |
| Dysentery<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Dysentery                 |                 |
|   | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |
|   | 1   | 0               |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Ear infection             |                 |
|   | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%) |
|   | 1   | 1               |
| Erysipelas<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Erysipelas                |                 |
|   | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |
|   | 1   | 0               |
| Erythema migrans<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Erythema migrans          |                 |
|   | 1 / 278 (0.36%)                                   | 0 / 279 (0.00%) |
|   | 1   | 0               |
| Febrile infection<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Febrile infection         |                 |
|   | 7 / 278 (2.52%)                                   | 7 / 279 (2.51%) |
|   | 7   | 7               |
| Fungal infection<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Fungal infection          |                 |
|   | 1 / 278 (0.36%)                                   | 1 / 279 (0.36%) |
|   | 1   | 1               |
| Fungal skin infection<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Fungal skin infection     |                 |
|   | 1 / 278 (0.36%)                                   | 2 / 279 (0.72%) |
|   | 1   | 2               |

|  |  |                         |
|--|--|-------------------------|
| Furuncle<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Furuncle                           |                         |
|  | 0 / 278 (0.00%)<br>0                                       | 1 / 279 (0.36%)<br>1    |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Gastroenteritis                    |                         |
|  | 2 / 278 (0.72%)<br>2                                       | 3 / 279 (1.08%)<br>3    |
| Gastrointestinal infection<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Gastrointestinal infection         |                         |
|  | 3 / 278 (1.08%)<br>3                                       | 3 / 279 (1.08%)<br>3    |
| Gastroenteritis norovirus<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Gastroenteritis norovirus          |                         |
|  | 0 / 278 (0.00%)<br>0                                       | 1 / 279 (0.36%)<br>1    |
| Gingivitis<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Gingivitis                         |                         |
|  | 1 / 278 (0.36%)<br>1                                       | 0 / 279 (0.00%)<br>0    |
| Genital infection fungal<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Genital infection fungal           |                         |
|  | 1 / 278 (0.36%)<br>1                                       | 0 / 279 (0.00%)<br>0    |
| H1N1 influenza<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: H1N1 influenza                     |                         |
|  | 1 / 278 (0.36%)<br>1                                       | 0 / 279 (0.00%)<br>0    |
| Hepatitis E<br>subjects affected / exposed<br>occurrences (all)                        | Additional description: Hepatitis E                        |                         |
|  | 1 / 278 (0.36%)<br>1                                       | 0 / 279 (0.00%)<br>0    |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Herpes zoster                      |                         |
|  | 16 / 278 (5.76%)<br>19                                     | 31 / 279 (11.11%)<br>34 |
| Herpes virus infection<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Herpes virus infection             |                         |
|  | 5 / 278 (1.80%)<br>6                                       | 9 / 279 (3.23%)<br>12   |
| Herpes simplex<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Herpes simplex                     |                         |
|  | 0 / 278 (0.00%)<br>0                                       | 1 / 279 (0.36%)<br>1    |
| Infection susceptibility increased<br>subjects affected / exposed<br>occurrences (all) | Additional description: Infection susceptibility increased |                         |
|  | 0 / 278 (0.00%)<br>0                                       | 1 / 279 (0.36%)<br>1    |

|  |  |                   |
|--|--|-------------------|
| Infection<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Infection              |                   |
|  | 18 / 278 (6.47%)                               | 12 / 279 (4.30%)  |
|  | 20   | 12                |
| Infected varicose vein<br>subjects affected / exposed<br>occurrences (all) | Additional description: Infected varicose vein |                   |
|  | 0 / 278 (0.00%)                                | 1 / 279 (0.36%)   |
|  | 0  | 1                 |
| Infected bites<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Infected bites         |                   |
|  | 1 / 278 (0.36%)                                | 0 / 279 (0.00%)   |
|  | 1  | 0                 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Influenza              |                   |
|  | 10 / 278 (3.60%)                               | 5 / 279 (1.79%)   |
|  | 11   | 5                 |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Laryngitis             |                   |
|  | 2 / 278 (0.72%)                                | 1 / 279 (0.36%)   |
|  | 2  | 1                 |
| Laryngitis bacterial<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Laryngitis bacterial   |                   |
|  | 0 / 278 (0.00%)                                | 1 / 279 (0.36%)   |
|  | 0  | 1                 |
| Localised infection<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Localised infection    |                   |
|  | 4 / 278 (1.44%)                                | 2 / 279 (0.72%)   |
|  | 4  | 2                 |
| Lung infection<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Lung infection         |                   |
|  | 0 / 278 (0.00%)                                | 1 / 279 (0.36%)   |
|  | 0  | 1                 |
| Lyme disease<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Lyme disease           |                   |
|  | 0 / 278 (0.00%)                                | 1 / 279 (0.36%)   |
|  | 0  | 1                 |
| Mastitis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Mastitis               |                   |
|  | 0 / 278 (0.00%)                                | 1 / 279 (0.36%)   |
|  | 0  | 1                 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Nasopharyngitis        |                   |
|  | 52 / 278 (18.71%)                              | 52 / 279 (18.64%) |
|  | 67   | 72                |
| Muscle abscess<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Muscle abscess         |                   |
|  | 0 / 278 (0.00%)                                | 1 / 279 (0.36%)   |
|  | 0  | 2                 |

|  |  |                        |
|--|--|------------------------|
| Oesophageal candidiasis<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Oesophageal candidiasis          |                        |
|  | 0 / 278 (0.00%)<br>0                                     | 1 / 279 (0.36%)<br>1   |
| Ophthalmic herpes zoster<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Ophthalmic herpes zoster         |                        |
|  | 1 / 278 (0.36%)<br>1                                     | 1 / 279 (0.36%)<br>1   |
| Oral fungal infection<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Oral fungal infection            |                        |
|  | 0 / 278 (0.00%)<br>0                                     | 1 / 279 (0.36%)<br>1   |
| Oral infection<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Oral infection                   |                        |
|  | 0 / 278 (0.00%)<br>0                                     | 1 / 279 (0.36%)<br>1   |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Oral herpes                      |                        |
|  | 17 / 278 (6.12%)<br>23                                   | 17 / 279 (6.09%)<br>19 |
| Otitis media<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Otitis media                     |                        |
|  | 2 / 278 (0.72%)<br>2                                     | 3 / 279 (1.08%)<br>3   |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Pharyngitis                      |                        |
|  | 9 / 278 (3.24%)<br>9                                     | 5 / 279 (1.79%)<br>5   |
| Pharyngeal chlamydia infection<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Pharyngeal chlamydia infection   |                        |
|  | 1 / 278 (0.36%)<br>1                                     | 0 / 279 (0.00%)<br>0   |
| Pneumocystis jirovecii pneumonia<br>subjects affected / exposed<br>occurrences (all) | Additional description: Pneumocystis jirovecii pneumonia |                        |
|  | 1 / 278 (0.36%)<br>1                                     | 0 / 279 (0.00%)<br>0   |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                        | Additional description: Pneumonia                        |                        |
|  | 13 / 278 (4.68%)<br>17                                   | 16 / 279 (5.73%)<br>16 |
| Postoperative wound infection<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Postoperative wound infection    |                        |
|  | 0 / 278 (0.00%)<br>0                                     | 1 / 279 (0.36%)<br>1   |
| Pulmonary mycosis<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Pulmonary mycosis                |                        |
|  | 0 / 278 (0.00%)<br>0                                     | 1 / 279 (0.36%)<br>1   |



|   |   |                        |
|---|---|------------------------|
| Pyelonephritis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Pyelonephritis              |                        |
|   | 1 / 278 (0.36%)<br>1                                | 0 / 279 (0.00%)<br>0   |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Respiratory tract infection |                        |
|   | 6 / 278 (2.16%)<br>7                                | 15 / 279 (5.38%)<br>21 |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Rhinitis                    |                        |
|   | 5 / 278 (1.80%)<br>5                                | 6 / 279 (2.15%)<br>7   |
| Sinobronchitis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Sinobronchitis              |                        |
|   | 1 / 278 (0.36%)<br>1                                | 2 / 279 (0.72%)<br>3   |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Sinusitis                   |                        |
|   | 10 / 278 (3.60%)<br>13                              | 19 / 279 (6.81%)<br>28 |
| Skin bacterial infection<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Skin bacterial infection    |                        |
|   | 1 / 278 (0.36%)<br>1                                | 2 / 279 (0.72%)<br>2   |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Skin infection              |                        |
|   | 1 / 278 (0.36%)<br>1                                | 3 / 279 (1.08%)<br>3   |
| Staphylococcal infection<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Staphylococcal infection    |                        |
|   | 0 / 278 (0.00%)<br>0                                | 1 / 279 (0.36%)<br>1   |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Tooth abscess               |                        |
|   | 0 / 278 (0.00%)<br>0                                | 2 / 279 (0.72%)<br>2   |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Tooth infection             |                        |
|   | 2 / 278 (0.72%)<br>2                                | 3 / 279 (1.08%)<br>3   |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Tonsillitis                 |                        |
|   | 3 / 278 (1.08%)<br>3                                | 3 / 279 (1.08%)<br>3   |
| Tracheobronchitis<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Tracheobronchitis           |                        |
|   | 0 / 278 (0.00%)<br>0                                | 2 / 279 (0.72%)<br>2   |

|  |   |                   |  |
|--|---|-------------------|--|
| Vaginal infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Vaccination site infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Varicella<br>subjects affected / exposed<br>occurrences (all)<br><br>Viral infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Wound infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Vaginal infection                 |                   |  |
|  | 0 / 278 (0.00%)   | 1 / 279 (0.36%)   |  |
|  | 0   | 1                 |  |
|  | Additional description: Urinary tract infection           |                   |  |
|  | 16 / 278 (5.76%)  | 12 / 279 (4.30%)  |  |
|  | 18  | 23                |  |
|  | Additional description: Upper respiratory tract infection |                   |  |
|  | 25 / 278 (8.99%)  | 50 / 279 (17.92%) |  |
|  | 32  | 75                |  |
|  | Additional description: Vaccination site infection        |                   |  |
|  | 1 / 278 (0.36%)   | 0 / 279 (0.00%)   |  |
|  | 1   | 0                 |  |
|  | Additional description: Varicella                         |                   |  |
|  | 1 / 278 (0.36%)   | 1 / 279 (0.36%)   |  |
|  | 1   | 1                 |  |
|  | Additional description: Viral infection                   |                   |  |
|  | 4 / 278 (1.44%)   | 5 / 279 (1.79%)   |  |
|  | 4   | 5                 |  |
|  | Additional description: Wound infection                   |                   |  |
|  | 1 / 278 (0.36%)   | 0 / 279 (0.00%)   |  |
|  | 1   | 0                 |  |
| Metabolism and nutrition disorders   |   |                   |  |
| Decreased appetite   | Additional description: Decreased appetite                |                   |  |
|  | 1 / 278 (0.36%)   | 1 / 279 (0.36%)   |  |
|  | 1   | 1                 |  |
| Folate deficiency  | Additional description: Folate deficiency                 |                   |  |
|  | 0 / 278 (0.00%)   | 1 / 279 (0.36%)   |  |
|  | 0   | 6                 |  |
| Gout   | Additional description: Gout                              |                   |  |
|  | 1 / 278 (0.36%)   | 0 / 279 (0.00%)   |  |
|  | 1   | 0                 |  |
| Hypercholesterolaemia  | Additional description: Hypercholesterolaemia             |                   |  |
|  | 0 / 278 (0.00%)   | 1 / 279 (0.36%)   |  |
|  | 0   | 1                 |  |
| Hyperglycaemia   | Additional description: Hyperglycaemia                    |                   |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 0 / 278 (0.00%)                                | 2 / 279 (0.72%) |  |
| occurrences (all)           | 0  | 3               |  |
| Hyperkalaemia               | Additional description: Hyperkalaemia          |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 0  | 1               |  |
| Iron overload               | Additional description: Iron overload          |                 |  |
| subjects affected / exposed | 0 / 278 (0.00%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 0  | 2               |  |
| Vitamin B12 deficiency      | Additional description: Vitamin B12 deficiency |                 |  |
| subjects affected / exposed | 1 / 278 (0.36%)                                | 1 / 279 (0.36%) |  |
| occurrences (all)           | 1  | 6               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 25 June 2010 | Global Amendment with German Protocol version 3.1 and date 25.06.2010 was submitted separately in each Country. |

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/27216274>