



## Clinical trial results:

### A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042) Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2014-001473-14             |
| Trial protocol           | SE CZ LT LV PT PL EE BG HU |
| Global end of trial date | 02 February 2023           |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 23 September 2023 |
| First version publication date | 23 September 2023 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 3475-042 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02220894 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck Sharp & Dohme LLC  |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065                   |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<br>ClinicalTrialsDisclosure@merck.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 02 February 2023  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 04 September 2018 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 02 February 2023  |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To compare the overall survival (OS) in subjects with TPS $\geq$ 50%, advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies, to compare the OS in subjects with TPS $\geq$ 20%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies and to compare the OS in subjects with TPS $\geq$ 1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 30 October 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 40          |
| Country: Number of subjects enrolled | Brazil: 113            |
| Country: Number of subjects enrolled | Bulgaria: 2            |
| Country: Number of subjects enrolled | Canada: 25             |
| Country: Number of subjects enrolled | Chile: 42              |
| Country: Number of subjects enrolled | China: 92              |
| Country: Number of subjects enrolled | Colombia: 8            |
| Country: Number of subjects enrolled | Czechia: 39            |
| Country: Number of subjects enrolled | Estonia: 12            |
| Country: Number of subjects enrolled | Guatemala: 11          |
| Country: Number of subjects enrolled | Hong Kong: 13          |
| Country: Number of subjects enrolled | Hungary: 3             |
| Country: Number of subjects enrolled | Japan: 93              |
| Country: Number of subjects enrolled | Korea, Republic of: 39 |
| Country: Number of subjects enrolled | Latvia: 49             |
| Country: Number of subjects enrolled | Lithuania: 30          |
| Country: Number of subjects enrolled | Malaysia: 35           |
| Country: Number of subjects enrolled | Mexico: 32             |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Peru: 23               |
| Country: Number of subjects enrolled | Philippines: 22        |
| Country: Number of subjects enrolled | Poland: 90             |
| Country: Number of subjects enrolled | Portugal: 12           |
| Country: Number of subjects enrolled | Romania: 26            |
| Country: Number of subjects enrolled | Russian Federation: 90 |
| Country: Number of subjects enrolled | South Africa: 34       |
| Country: Number of subjects enrolled | Sweden: 7              |
| Country: Number of subjects enrolled | Switzerland: 16        |
| Country: Number of subjects enrolled | Taiwan: 22             |
| Country: Number of subjects enrolled | Thailand: 52           |
| Country: Number of subjects enrolled | Turkey: 109            |
| Country: Number of subjects enrolled | Ukraine: 91            |
| Country: Number of subjects enrolled | Viet Nam: 2            |
| Worldwide total number of subjects   | 1274                   |
| EEA total number of subjects         | 270                    |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 707 |
| From 65 to 84 years                       | 554 |
| 85 years and over                         | 13  |

## Subject disposition

### Recruitment

Recruitment details:

Of the 1275 participants randomized (pembrolizumab=638, chemotherapy=637), 1 participant assigned to receive pembrolizumab died prior to randomization and was randomized in error. The intent to treat population was defined as participants alive at the time of randomization, so the actual randomized population included 637 participants in each arm.

### Pre-assignment

Screening details:

Pembrolizumab-treated participants, who attained a complete response (CR) or who stopped treatment after 35 administrations for reasons other than disease progression or intolerability may have been eligible for re-treatment with pembrolizumab after they had experienced radiographic disease as per protocol-defined criteria.

### Period 1

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

### Arms

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

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) for a maximum of 35 cycles (21-day cycles). Some participants may have been eligible for re-treatment with pembrolizumab monotherapy after they had experienced radiographic disease as per protocol-defined criteria.

|  |                      |
|--|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Pembrolizumab        |
| Investigational medicinal product code |                      |
| Other name                             | MK-3475<br>KEYTRUDA® |
| Pharmaceutical forms                   | Infusion, Infusion   |
| Routes of administration               | Intravenous use      |

Dosage and administration details:

200 mg on Day 1 of every 21-day cycle (every 3 weeks, or Q3W) for up to 35 treatments

|                  |   |
|------------------|---|
| <b>Arm title</b> | Chemotherapy (Standard of Care [SOC] Treatment) |
|------------------|---|

Arm description:

Participants received carboplatin at target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m<sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m<sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m<sup>2</sup> by IV infusion on Day 1 Q3W

|  |                       |
|--|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             | PARAPLATIN®           |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Carboplatin target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose

900 mg)

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | pemetrexed            |
| Investigational medicinal product code |                       |
| Other name                             | ALIMTA®               |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

500 mg/m<sup>2</sup> IV on Day 1 Q3W for a maximum of 6 cycles

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             | TAXOL®                |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

200 mg/m<sup>2</sup> IV on Day 1 of every 21-day cycle (Q3W) for a maximum of 6 cycles

| Number of subjects in period 1               | Pembrolizumab | Chemotherapy<br>(Standard of Care<br>[SOC] Treatment) |
|--|---------------|---|
|  |               |   |
| Started                                      | 637           | 637   |
| Treated                                      | 636           | 615   |
| Completed                                    | 0             | 0   |
| Not completed                                | 637           | 637   |
| Adverse event, serious fatal                 | 418           | 508   |
| Consent withdrawn by subject                 | 10            | 9   |
| Adverse event, non-fatal                     | 127           | 74  |
| Withdrawal by Parent/Guardian                | -             | 1   |
| Site Terminated by Sponsor                   | 2             | -   |
| Participation in Study Terminated by Sponsor | 80            | 41  |
| Lost to follow-up                            | -             | 4   |

## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | Pembrolizumab                                   |
| Reporting group description:  |   |
| Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) for a maximum of 35 cycles (21-day cycles). Some participants may have been eligible for re-treatment with pembrolizumab monotherapy after they had experienced radiographic disease as per protocol-defined criteria.   |   |
| Reporting group title   | Chemotherapy (Standard of Care [SOC] Treatment) |
| Reporting group description:  |   |
| Participants received carboplatin at target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m <sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m <sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m <sup>2</sup> by IV infusion on Day 1 Q3W |   |

| Reporting group values  | Pembrolizumab | Chemotherapy (Standard of Care [SOC] Treatment) | Total |
|---|---------------|---|-------|
| Number of subjects  | 637           | 637   | 1274  |
| Age categorical<br>Units: Subjects  |               |   |       |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |               |   |       |
| Age Continuous<br>Units: Years  |               |   |       |
| arithmetic mean   | 62.5          | 63.1  | -     |
| standard deviation  | ± 9.9         | ± 9.4   | -     |
| Sex: Female, Male<br>Units: Participants  |               |   |       |
| Female  | 187           | 185   | 372   |
| Male  | 450           | 452   | 902   |
| Race (NIH/OMB)<br>Units: Subjects   |               |   |       |
| American Indian or Alaska Native  | 10            | 5   | 15    |
| Asian   | 189           | 187   | 376   |
| Native Hawaiian or Other Pacific Islander   | 0             | 1   | 1     |
| Black or African American   | 10            | 13  | 23    |
| White   | 398           | 412   | 810   |
| More than one race  | 30            | 19  | 49    |
| Eastern Cooperative Oncology Group  |               |   |       |

|  |     |     |     |
|--|-----|-----|-----|
| (ECOG) Performance Status (PS)   |     |     |     |
| Participants were assessed for ECOG PS: Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory & able to carry out work of a light or sedentary nature; Grade 2: Ambulatory & capable of all selfcare but unable to carry out any work activities, up & about more than 50% of waking hours; Grade 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4: Completely disabled, cannot carry on any selfcare, totally confined to bed or chair or Grade 5: Dead. |     |     |     |
| Units: Subjects  |     |     |     |
| ECOG PS=0  | 197 | 192 | 389 |
| ECOG PS=1  | 439 | 445 | 884 |
| ECOG PS=2  | 1   | 0   | 1   |
| Programmed Cell Death-Ligand 1 (PD-L1) Tumor Status  |     |     |     |
| Participants were assessed for their PD-L1 tumor expression status by immunohistochemistry assay using tumor tissue from an archival or newly obtained biopsy. Participants with a tumor proportion score (TPS) were classified as follows: $\geq 50\%$ = PD-L1 strongly positive; 1-49% = PD-L1 weakly positive; and $< 1\%$ = PD-L1 negative.  |     |     |     |
| Units: Subjects  |     |     |     |
| TPS= $\geq 50\%$   | 299 | 300 | 599 |
| TPS=20-49%   | 114 | 105 | 219 |
| TPS=1-19%  | 224 | 232 | 456 |
| TPS= $< 1\%$   | 0   | 0   | 0   |
| Tumor Histology  |     |     |     |
| Participants were classified according to tumor histology: Squamous or Non-squamous. The tumor histology determined potential treatment regimen.   |     |     |     |
| Units: Subjects  |     |     |     |
| Squamous   | 242 | 249 | 491 |
| Non-squamous   | 395 | 388 | 783 |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Pembrolizumab                                   |
| Reporting group description:  |   |
| Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) for a maximum of 35 cycles (21-day cycles). Some participants may have been eligible for re-treatment with pembrolizumab monotherapy after they had experienced radiographic disease as per protocol-defined criteria.   |   |
| Reporting group title   | Chemotherapy (Standard of Care [SOC] Treatment) |
| Reporting group description:  |   |
| Participants received carboplatin at target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m <sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m <sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m <sup>2</sup> by IV infusion on Day 1 Q3W |   |

### Primary: Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of $\geq 50\%$

|  |  |
|--|--|
| End point title  | Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of $\geq 50\%$ |
| End point description:   |  |
| OS was determined for participants with a TPS of $\geq 50\%$ and was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was OS in participants with TPS $\geq 50\%$ , then with TPS $\geq 20\%$ , and finally with TPS $\geq 1\%$ . The OS for participants with a TPS $\geq 50\%$ is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of $\geq 50\%$ . |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Up to 45 months  |  |

| End point values                 | Pembrolizumab       | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|----------------------------------|---------------------|---|--|--|
| Subject group type               | Reporting group     | Reporting group                                 |  |  |
| Number of subjects analysed      | 299                 | 300   |  |  |
| Units: Months                    |                     |   |  |  |
| median (confidence interval 95%) | 20.0 (15.9 to 24.2) | 12.2 (10.4 to 14.6)                             |  |  |

### Statistical analyses



|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Pembrolizumab vs SOC  |
| Statistical analysis description:<br>Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). |   |
| Comparison groups   | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis   | 599   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0003 <sup>[1]</sup>   |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.7   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.58  |
| upper limit   | 0.86  |

Notes:

[1] - One-sided p-value based on stratified log-rank test

### Primary: Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of $\geq 20\%$

|                 |  |
|-----------------|--|
| End point title | Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of $\geq 20\%$ |
|-----------------|--|

End point description:

OS was determined for participants with a TPS of  $\geq 20\%$  and was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was OS in participants with TPS  $\geq 50\%$ , then with TPS  $\geq 20\%$ , and finally with TPS  $\geq 1\%$ . The OS for participants with a TPS  $\geq 20\%$  is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of  $\geq 20\%$ .

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 45 months

| <b>End point values</b>          | Pembrolizumab       | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|----------------------------------|---------------------|---|--|--|
| Subject group type               | Reporting group     | Reporting group                                 |  |  |
| Number of subjects analysed      | 413                 | 405   |  |  |
| Units: Months                    |                     |   |  |  |
| median (confidence interval 95%) | 18.0 (15.4 to 21.9) | 13.0 (11.6 to 15.3)                             |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Pembrolizumab vs SOC  |
| Statistical analysis description:  |   |
| Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). |   |
| Comparison groups  | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis  | 818   |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.0012 <sup>[2]</sup>   |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.77  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.65  |
| upper limit  | 0.91  |

Notes:

[2] - One-sided p-value based on stratified log-rank test

### Primary: Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of $\geq 1\%$

|   |   |
|---|---|
| End point title   | Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of $\geq 1\%$ |
| End point description:  |   |
| OS was determined for participants with a TPS of $\geq 1\%$ and was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was OS in participants with TPS $\geq 50\%$ , then with TPS $\geq 20\%$ , and finally with TPS $\geq 1\%$ . The OS for participants with a TPS $\geq 1\%$ is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of $\geq 1\%$ . |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Up to 45 months   |   |

| End point values                 | Pembrolizumab       | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|----------------------------------|---------------------|---|--|--|
| Subject group type               | Reporting group     | Reporting group                                 |  |  |
| Number of subjects analysed      | 637                 | 637   |  |  |
| Units: Months                    |                     |   |  |  |
| median (confidence interval 95%) | 16.4 (14.0 to 19.7) | 12.1 (11.3 to 13.3)                             |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Pembrolizumab vs SOC  |
| Statistical analysis description:<br>Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). |   |
| Comparison groups   | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis   | 1274  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0013 <sup>[3]</sup>   |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.82  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.71  |
| upper limit   | 0.93  |

Notes:

[3] - One-sided p-value based on stratified log-rank test

## Secondary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of $\geq 20\%$

|                 |   |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of $\geq 20\%$ |
|-----------------|---|

End point description:

PFS was determined for participants with a TPS of  $\geq 20\%$  and was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as  $\geq 20\%$  increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of  $\geq 5$  mm. The appearance of 1 or more new lesions was also considered PD. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was PFS in participants with  $\text{TPS} \geq 50\%$ , then with  $\text{TPS} \geq 20\%$ , and finally with  $\text{TPS} \geq 1\%$ . The PFS for participants with a  $\text{TPS} \geq 20\%$  is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of  $\geq 20\%$ .

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 45 months      |           |

|                                  |                  |   |  |  |
|----------------------------------|------------------|---|--|--|
| <b>End point values</b>          | Pembrolizumab    | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
| Subject group type               | Reporting group  | Reporting group                                 |  |  |
| Number of subjects analysed      | 413              | 405   |  |  |
| Units: Months                    |                  |   |  |  |
| median (confidence interval 95%) | 6.2 (5.1 to 7.4) | 6.7 (6.3 to 8.0)                                |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Pembrolizumab vs SOC  |
| Statistical analysis description:  |   |
| Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). |   |
| Comparison groups  | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis  | 818   |
| Analysis specification   | Pre-specified   |
| Analysis type  |   |
| P-value  | = 0.2134 <sup>[4]</sup>   |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.94  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.8   |
| upper limit  | 1.1   |

Notes:

[4] - One-sided p-value based on stratified log-rank test

## Secondary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50%

|                 |  |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50% |
|-----------------|--|

End point description:

PFS was determined for participants with a TPS of ≥50% and was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of 1 or more new lesions was also considered PD. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was PFS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The PFS for participants with a TPS ≥50% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥50%.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 45 months      |           |

|                                  |                  |   |  |  |
|----------------------------------|------------------|---|--|--|
| <b>End point values</b>          | Pembrolizumab    | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
| Subject group type               | Reporting group  | Reporting group                                 |  |  |
| Number of subjects analysed      | 299              | 300   |  |  |
| Units: Months                    |                  |   |  |  |
| median (confidence interval 95%) | 6.5 (5.9 to 8.5) | 6.4 (6.2 to 7.2)                                |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Pembrolizumab vs SOC  |
| Statistical analysis description:  |   |
| Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). |   |
| Comparison groups  | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis  | 599   |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.026 <sup>[5]</sup>  |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.83  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.69  |
| upper limit  | 1   |

Notes:

[5] - One-sided p-value based on stratified log-rank test

## Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50%

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50% |
|-----------------|--|

End point description:

ORR was determined for participants with a TPS of ≥50%. ORR was determined per RECIST 1.1 and was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was ORR in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The percentage of participants who had a TPS ≥50% and who experienced a CR or PR is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥50%.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 45 months      |           |

|                                   |                     |   |  |  |
|-----------------------------------|---------------------|---|--|--|
| <b>End point values</b>           | Pembrolizumab       | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
| Subject group type                | Reporting group     | Reporting group                                 |  |  |
| Number of subjects analysed       | 299                 | 300   |  |  |
| Units: Percentage of participants |                     |   |  |  |
| number (confidence interval 95%)  | 39.1 (33.6 to 44.9) | 32.0 (26.8 to 37.6)                             |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Pembrolizumab vs SOC  |
| Statistical analysis description:  |   |
| Difference in Percentage (DP) for pembrolizumab vs. chemotherapy based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. nonsquamous). |   |
| Comparison groups  | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis  | 599   |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.0353 <sup>[6]</sup>   |
| Method   | Stratified Miettinen and Nurminen                               |
| Parameter estimate   | Difference in Percentage (DP)                                   |
| Point estimate   | 7   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -0.6  |
| upper limit  | 14.6  |

Notes:

[6] - One-sided p-value for testing. H0: difference in percentages=0 vs. H1: difference in percentages >0

## Secondary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥1%

|                 |   |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥1% |
|-----------------|---|

End point description:

PFS was determined for participants with a TPS of ≥1% and was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an

absolute increase of  $\geq 5$  mm. The appearance of 1 or more new lesions was also considered PD. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was PFS in participants with  $\text{TPS} \geq 50\%$ , then with  $\text{TPS} \geq 20\%$ , and finally with  $\text{TPS} \geq 1\%$ . The PFS for participants with a  $\text{TPS} \geq 1\%$  is presented. The analysis population included all participants who were alive at the time of randomization and had a  $\text{TPS} \geq 1\%$ .

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 45 months      |           |

| End point values                 | Pembrolizumab    | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|----------------------------------|------------------|---|--|--|
| Subject group type               | Reporting group  | Reporting group                                 |  |  |
| Number of subjects analysed      | 637              | 637   |  |  |
| Units: Months                    |                  |   |  |  |
| median (confidence interval 95%) | 5.4 (4.3 to 6.2) | 6.6 (6.3 to 7.3)                                |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Pembrolizumab vs SOC  |
| Statistical analysis description:   |   |
| Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status ( $\text{TPS} \geq 50\%$ vs. $\text{TPS} = 1\text{-}49\%$ ) and histology (squamous vs. non-squamous). |   |
| Comparison groups   | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis   | 1274  |
| Analysis specification  | Pre-specified   |
| Analysis type   |   |
| P-value   | = 0.7964 <sup>[7]</sup>   |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 1.05  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.93  |
| upper limit   | 1.19  |

Notes:

[7] - One-sided p-value based on stratified log-rank test

## Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of $\geq 20\%$

|                 |   |
|-----------------|---|
| End point title | Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of $\geq 20\%$ |
|-----------------|---|

**End point description:**

ORR was determined for participants with a TPS of  $\geq 20\%$ . ORR was determined per RECIST 1.1 and was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR:  $\geq 30\%$  decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was ORR in participants with  $\text{TPS} \geq 50\%$ , then with  $\text{TPS} \geq 20\%$ , and finally with  $\text{TPS} \geq 1\%$ . The percentage of participants who had a  $\text{TPS} \geq 20\%$  and who experienced a CR or PR is presented. The analysis population included all participants who were alive at the time of randomization and had a  $\text{TPS}$  of  $\geq 20\%$ .

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 45 months      |           |

| End point values                  | Pembrolizumab       | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|-----------------------------------|---------------------|---|--|--|
| Subject group type                | Reporting group     | Reporting group                                 |  |  |
| Number of subjects analysed       | 413                 | 405   |  |  |
| Units: Percentage of participants |                     |   |  |  |
| number (confidence interval 95%)  | 33.2 (28.6 to 37.9) | 28.9 (24.5 to 33.6)                             |  |  |

**Statistical analyses**

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Pembrolizumab vs SOC |
|----------------------------|----------------------|

**Statistical analysis description:**

DP for pembrolizumab vs. chemotherapy based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status ( $\text{TPS} \geq 50\%$  vs.  $\text{TPS} = 1\text{--}49\%$ ) and histology (squamous vs. non-squamous).

|   |   |
|---|---|
| Comparison groups                       | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis | 818   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0744 <sup>[8]</sup>   |
| Method                                  | Stratified Miettinen and Nurminen                               |
| Parameter estimate                      | Difference in Percentage (DP)                                   |
| Point estimate                          | 4.6   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.7  |
| upper limit                             | 10.9  |

**Notes:**

[8] - One-sided p-value for testing. H0: difference in percentages=0 vs. H1: difference in percentages >0

**Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in**



**Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of  $\geq 1\%$** 

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of $\geq 1\%$ |
|-----------------|--|

## End point description:

ORR was determined for participants with a TPS of  $\geq 1\%$ . ORR was determined per RECIST 1.1 and was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR:  $\geq 30\%$  decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was ORR in participants with  $\text{TPS} \geq 50\%$ , then with  $\text{TPS} \geq 20\%$ , and finally with  $\text{TPS} \geq 1\%$ . The percentage of participants who had a  $\text{TPS} \geq 1\%$  and who experienced a CR or PR is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of  $\geq 1\%$ .

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

## End point timeframe:

Up to 45 months

| End point values                  | Pembrolizumab       | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|-----------------------------------|---------------------|---|--|--|
| Subject group type                | Reporting group     | Reporting group                                 |  |  |
| Number of subjects analysed       | 637                 | 637   |  |  |
| Units: Percentage of participants |                     |   |  |  |
| number (confidence interval 95%)  | 27.2 (23.7 to 30.8) | 26.5 (23.1 to 30.1)                             |  |  |

**Statistical analyses**

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Pembrolizumab vs SOC |
|----------------------------|----------------------|

## Statistical analysis description:

DP for pembrolizumab vs. chemotherapy based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status ( $\text{TPS} \geq 50\%$  vs.  $\text{TPS} = 1-49\%$ ) and histology (squamous vs. non-squamous).

|   |   |
|---|---|
| Comparison groups                       | Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment) |
| Number of subjects included in analysis | 1274  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.406 <sup>[9]</sup>  |
| Method                                  | Stratified Miettinen and Nurminen                               |
| Parameter estimate                      | Difference in Percentage (DP)                                   |
| Point estimate                          | 0.6   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.2  |
| upper limit                             | 5.4   |

Notes:

[9] - One-sided p-value for testing. H0: difference in percentages=0 vs. H1: difference in percentages >0

## Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE)

|                 |  |
|-----------------|--|
| End point title | Number of Participants Who Experienced At Least One Adverse Event (AE) |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. The number of participants who experienced at least one AE is presented. The analysis population consisted of all participants who received  $\geq 1$  dose of study treatment.

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

End point timeframe:

Up to 93 months

| End point values            | Pembrolizumab   | Chemotherapy (Standard of Care [SOC] Treatment) |  |  |
|-----------------------------|-----------------|---|--|--|
| Subject group type          | Reporting group | Reporting group                                 |  |  |
| Number of subjects analysed | 636             | 615   |  |  |
| Units: Participants         | 608             | 606   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)

|                 |  |
|-----------------|--|
| End point title | Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE) |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. The number of participants who discontinued study treatment due to an AE is presented. The analysis population consisted of all participants who received  $\geq 1$  dose of study treatment.

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

End point timeframe:

Up to 93 months

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Pembrolizumab   | Chemotherapy<br>(Standard of<br>Care [SOC]<br>Treatment) |  |  |
| Subject group type          | Reporting group | Reporting group  |  |  |
| Number of subjects analysed | 636             | 615  |  |  |
| Units: Participants         | 126             | 93   |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 93 months

Adverse event reporting additional description:

Population: All participants receiving  $\geq 1$  dose of study treatment. Per protocol, progression of cancer under study was not considered an AE unless related to study drug. Therefore, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" not related to study drug are excluded as AEs.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Pembrolizumab |
|-----------------------|---------------|

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 Q3W for a maximum of 35 cycles (21-day cycles)

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Pembrolizumab Second Course |
|-----------------------|-----------------------------|

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Chemotherapy (SOC Treatment) |
|-----------------------|------------------------------|

Reporting group description:

Participants received carboplatin at target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m<sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m<sup>2</sup> by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m<sup>2</sup> by IV infusion on Day 1 Q3W.

| Serious adverse events  | Pembrolizumab      | Pembrolizumab Second Course | Chemotherapy (SOC Treatment) |
|---|--------------------|-----------------------------|------------------------------|
| Total subjects affected by serious adverse events                   |                    |                             |                              |
| subjects affected / exposed   | 261 / 636 (41.04%) | 8 / 34 (23.53%)             | 193 / 615 (31.38%)           |
| number of deaths (all causes)                                       | 528                | 18                          | 582                          |
| number of deaths resulting from adverse events                      | 13                 | 0                           | 14                           |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                             |                              |
| Malignant neoplasm progression                                      |                    |                             |                              |
| subjects affected / exposed   | 2 / 636 (0.31%)    | 0 / 34 (0.00%)              | 0 / 615 (0.00%)              |
| occurrences causally related to treatment / all                     | 2 / 2              | 0 / 0                       | 0 / 0                        |
| deaths causally related to treatment / all                          | 2 / 2              | 0 / 0                       | 0 / 0                        |
| Metastases to bone  |                    |                             |                              |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Oesophageal carcinoma                           |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Adenocarcinoma gastric                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Keratoacanthoma                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cancer pain                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric cancer                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infected neoplasm                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Anogenital warts                                |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Lung cancer metastatic                          |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Lung neoplasm malignant                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Squamous cell carcinoma                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Squamous cell carcinoma of the tongue           |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Tumour necrosis                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Tumour associated fever                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 1 / 34 (2.94%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vascular disorders                              |                 |                |                 |
| Hypertension                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Superior vena cava syndrome                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| Aortic aneurysm                                 |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Arterial thrombosis                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Deep vein thrombosis                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Peripheral ischaemia                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypotension                                     |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Jugular vein thrombosis                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Peripheral artery occlusion                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Embolism  |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Venous thrombosis                               |                 |                |                 |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed                          | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                 |                |                 |
| Death  |                 |                |                 |
| subjects affected / exposed                          | 9 / 636 (1.42%) | 0 / 34 (0.00%) | 5 / 615 (0.81%) |
| occurrences causally related to treatment / all      | 1 / 9           | 0 / 0          | 0 / 5           |
| deaths causally related to treatment / all           | 1 / 9           | 0 / 0          | 0 / 5           |
| Fatigue  |                 |                |                 |
| subjects affected / exposed                          | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Malaise  |                 |                |                 |
| subjects affected / exposed                          | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Pyrexia  |                 |                |                 |
| subjects affected / exposed                          | 4 / 636 (0.63%) | 1 / 34 (2.94%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all      | 2 / 4           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Accidental death                                     |                 |                |                 |
| subjects affected / exposed                          | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0          | 0 / 0           |
| Asthenia   |                 |                |                 |
| subjects affected / exposed                          | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 4 / 615 (0.65%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 3 / 4           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Ill-defined disorder                                 |                 |                |                 |
| subjects affected / exposed                          | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Performance status decreased                         |                 |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Prosthetic cardiac valve thrombosis             |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Sudden death                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| General physical health deterioration           |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Immune system disorders                         |                 |                |                 |
| Anaphylactic reaction                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Contrast media allergy                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Reproductive system and breast disorders        |                 |                |                 |
| Benign prostatic hyperplasia                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Ovarian cyst torsion                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| Respiratory, thoracic and mediastinal disorders |                  |                |                  |
| Interstitial lung disease                       |                  |                |                  |
| subjects affected / exposed                     | 4 / 636 (0.63%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 6 / 6            | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Chronic obstructive pulmonary disease           |                  |                |                  |
| subjects affected / exposed                     | 2 / 636 (0.31%)  | 0 / 34 (0.00%) | 5 / 615 (0.81%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Haemoptysis                                     |                  |                |                  |
| subjects affected / exposed                     | 7 / 636 (1.10%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 1 / 7            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Pleural effusion                                |                  |                |                  |
| subjects affected / exposed                     | 14 / 636 (2.20%) | 0 / 34 (0.00%) | 5 / 615 (0.81%)  |
| occurrences causally related to treatment / all | 8 / 16           | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 1            |
| Pulmonary embolism                              |                  |                |                  |
| subjects affected / exposed                     | 13 / 636 (2.04%) | 0 / 34 (0.00%) | 11 / 615 (1.79%) |
| occurrences causally related to treatment / all | 2 / 13           | 0 / 0          | 5 / 11           |
| deaths causally related to treatment / all      | 1 / 5            | 0 / 0          | 1 / 5            |
| Respiratory failure                             |                  |                |                  |
| subjects affected / exposed                     | 4 / 636 (0.63%)  | 0 / 34 (0.00%) | 4 / 615 (0.65%)  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 1 / 3            | 0 / 0          | 0 / 3            |
| Acute respiratory failure                       |                  |                |                  |
| subjects affected / exposed                     | 2 / 636 (0.31%)  | 0 / 34 (0.00%) | 0 / 615 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 0            |
| Acute pulmonary oedema                          |                  |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Asthma  |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Atelectasis                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Bronchitis chronic                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Chronic respiratory failure                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pleurisy  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hydrothorax                                     |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Lung disorder                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Oesophagobronchial fistula                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Dyspnoea  |                 |                |                 |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| subjects affected / exposed                     | 7 / 636 (1.10%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 2 / 8            | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 1 / 1           |
| Pneumonitis                                     |                  |                |                 |
| subjects affected / exposed                     | 25 / 636 (3.93%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 26 / 26          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0          | 0 / 0           |
| Pneumothorax                                    |                  |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Pulmonary artery thrombosis                     |                  |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%)  | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0           |
| Pulmonary fistula                               |                  |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Pulmonary oedema                                |                  |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%)  | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 2           |
| Pulmonary thrombosis                            |                  |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Respiratory distress                            |                  |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%)  | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 1 / 1           |
| Tracheal stenosis                               |                  |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pulmonary haemorrhage                           |                 |                |                 |
| subjects affected / exposed                     | 4 / 636 (0.63%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 0          | 0 / 2           |
| Psychiatric disorders                           |                 |                |                 |
| Confusional state                               |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Delirium  |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Depression                                      |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Completed suicide                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Investigations                                  |                 |                |                 |
| Neutrophil count decreased                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 5 / 615 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 5 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Platelet count decreased                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Alanine aminotransferase increased              |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Aspartate aminotransferase increased            |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood prolactin increased                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood bilirubin increased                       |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood calcium decreased                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood pressure increased                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Bilirubin conjugated increased                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                |                 |
| Subdural haematoma                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cervical vertebral fracture                     |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Femur fracture                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hip fracture                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infusion related reaction                       |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Lumbar vertebral fracture                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Radius fracture                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Subdural haemorrhage                            |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 1 / 34 (2.94%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 0           |
| Upper limb fracture                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cardiac disorders                               |                 |                |                 |
| Coronary artery disease                         |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Myocardial infarction                           |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Acute coronary syndrome                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Acute myocardial infarction                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cardiac failure                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Arrhythmia                                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Atrial fibrillation                             |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Atrial flutter                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cardiac arrest                                  |                 |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0          | 0 / 1           |
| Aortic valve stenosis                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cardiac failure acute                           |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| Cardiac tamponade                               |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0          | 0 / 1           |
| Cardiopulmonary failure                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Myocarditis                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pericarditis                                    |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Sinus tachycardia                               |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Supraventricular tachycardia                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Ventricular fibrillation                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pericardial effusion                            |                 |                |                 |
| subjects affected / exposed                     | 6 / 636 (0.94%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 4 / 6           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                 |                |                 |
| Cerebral infarction                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Haemorrhage intracranial                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Dizziness                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cerebrovascular accident                        |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 1           |
| Altered state of consciousness                  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Ataxia  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cerebral ischaemia                              |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Coma  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Embolic stroke                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Encephalopathy                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| Epilepsy  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Psychomotor hyperactivity                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Ischaemic stroke                                |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Loss of consciousness                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Metabolic encephalopathy                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Neuropathy peripheral                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Headache  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Seizure   |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Spinal cord compression                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Syncope   |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Transient ischaemic attack                      |                 |                |                 |

|   |                 |                |                  |
|---|-----------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| <b>Blood and lymphatic system disorders</b>     |                 |                |                  |
| <b>Agranulocytosis</b>                          |                 |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| <b>Anaemia</b>                                  |                 |                |                  |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 16 / 615 (2.60%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 21 / 23          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| <b>Lymphadenopathy</b>                          |                 |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| <b>Neutropenia</b>                              |                 |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 8 / 615 (1.30%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 8 / 8            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| <b>Thrombocytopenia</b>                         |                 |                |                  |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 6 / 615 (0.98%)  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 6 / 6            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 1 / 1            |
| <b>Leukopenia</b>                               |                 |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 2 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| <b>Febrile neutropenia</b>                      |                 |                |                  |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 16 / 615 (2.60%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 14 / 17          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 1 / 1            |
| <b>Normochromic anaemia</b>                     |                 |                |                  |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Splenic infarction                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                |                 |
| Vertigo   |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                 |                |                 |
| Diarrhoea                                       |                 |                |                 |
| subjects affected / exposed                     | 5 / 636 (0.79%) | 1 / 34 (2.94%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all | 3 / 5           | 1 / 1          | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Dyspepsia                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Abdominal pain                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Colitis   |                 |                |                 |
| subjects affected / exposed                     | 6 / 636 (0.94%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 5 / 6           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Constipation                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Duodenal perforation                            |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Enterocolitis                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric haemorrhage                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric ulcer haemorrhage                       |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0          | 0 / 0           |
| Gastritis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Incarcerated inguinal hernia                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal ulcer                          |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Glossitis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Haematemesis                                    |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 1 / 34 (2.94%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 0           |
| Ileus paralytic                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Inguinal hernia                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intestinal ischaemia                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Melaena   |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nausea  |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 1 / 34 (2.94%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Oesophageal fistula                             |                 |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pancreatic mass                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Rectal ulcer                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Stomatitis                                      |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Neutropenic colitis                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Volvulus  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vomiting  |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                 |                |                 |
| Autoimmune hepatitis                            |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatic function abnormal                       |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatitis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatitis acute                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatitis toxic                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Immune-mediated hepatitis                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                |                 |
| Drug eruption                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Urticaria                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Rash  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 1 / 34 (2.94%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Rash maculo-papular                             |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                 |                |                 |
| Renal failure                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Acute kidney injury                             |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 4 / 615 (0.65%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 2 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Glomerulonephritis membranous                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hydronephrosis                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nephritis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nephropathy                                     |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Urinary retention                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal tubular necrosis                          |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Endocrine disorders                             |                 |                |                 |
| Adrenal insufficiency                           |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hyperthyroidism                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypophysitis                                    |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypopituitarism                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypothyroidism                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                |                 |
| Bone pain                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Neck pain                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Arthralgia                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Back pain                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Musculoskeletal chest pain                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Myalgia   |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Osteitis  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Osteoporotic fracture                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pain in extremity                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Rotator cuff syndrome                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                 |                |                 |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| Upper respiratory tract infection               |                  |                |                  |
| subjects affected / exposed                     | 1 / 636 (0.16%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Infection                                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 636 (0.16%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 1 / 1            |
| Lung abscess                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 636 (0.16%)  | 0 / 34 (0.00%) | 2 / 615 (0.33%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pneumonia                                       |                  |                |                  |
| subjects affected / exposed                     | 49 / 636 (7.70%) | 2 / 34 (5.88%) | 34 / 615 (5.53%) |
| occurrences causally related to treatment / all | 1 / 54           | 0 / 2          | 14 / 41          |
| deaths causally related to treatment / all      | 0 / 10           | 0 / 0          | 4 / 7            |
| Septic shock                                    |                  |                |                  |
| subjects affected / exposed                     | 3 / 636 (0.47%)  | 0 / 34 (0.00%) | 4 / 615 (0.65%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 2 / 4            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0          | 2 / 2            |
| Lymph gland infection                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%)  | 1 / 34 (2.94%) | 0 / 615 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Biliary sepsis                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 636 (0.00%)  | 0 / 34 (0.00%) | 1 / 615 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Abscess jaw                                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 636 (0.16%)  | 0 / 34 (0.00%) | 0 / 615 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Amoebiasis                                      |                  |                |                  |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Amoebic dysentery                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Anal abscess                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Abdominal sepsis                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Bronchitis                                      |                 |                |                 |
| subjects affected / exposed                     | 8 / 636 (1.26%) | 0 / 34 (0.00%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 0          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| COVID-19  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Candida infection                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cellulitis                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastroenteritis                                 |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cystitis  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Device related infection                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Diverticulitis                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Enterocolitis infectious                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Clostridium difficile infection                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastroenteritis viral                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Herpes zoster                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infectious pleural effusion                     |                 |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                                   | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Infective exacerbation of bronchiectasis                      |                 |                |                 |
| subjects affected / exposed                                   | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Oesophageal candidiasis                                       |                 |                |                 |
| subjects affected / exposed                                   | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Influenza   |                 |                |                 |
| subjects affected / exposed                                   | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all               | 0 / 2           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Laryngitis  |                 |                |                 |
| subjects affected / exposed                                   | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Lower respiratory tract infection                             |                 |                |                 |
| subjects affected / exposed                                   | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0          | 0 / 3           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Neutropenic sepsis  |                 |                |                 |
| subjects affected / exposed                                   | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 1 / 1           |
| Infective exacerbation of chronic obstructive airways disease |                 |                |                 |
| subjects affected / exposed                                   | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0          | 0 / 0           |
| Peritonitis   |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pleural infection                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumocystis jirovecii pneumonia                |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumonia aspiration                            |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumonia bacterial                             |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 1 / 34 (2.94%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Sepsis  |                 |                |                 |
| subjects affected / exposed                     | 4 / 636 (0.63%) | 0 / 34 (0.00%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0          | 3 / 4           |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 0          | 0 / 0           |
| Post procedural cellulitis                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pseudomembranous colitis                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pulmonary sepsis                                |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 1 / 2           |
| Respiratory tract infection                     |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Pneumonia klebsiella                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vascular access site infection                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Viral infection                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                |                 |
| Decreased appetite                              |                 |                |                 |
| subjects affected / exposed                     | 4 / 636 (0.63%) | 0 / 34 (0.00%) | 3 / 615 (0.49%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0          | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Electrolyte imbalance                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hyperuricaemia                                  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hyponatraemia                                   |                 |                |                 |
| subjects affected / exposed                     | 3 / 636 (0.47%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Ketoacidosis                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 1 / 1           |
| Diabetes mellitus                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Type 2 diabetes mellitus                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 636 (0.00%) | 0 / 34 (0.00%) | 1 / 615 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Dehydration                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypercalcaemia                                  |                 |                |                 |
| subjects affected / exposed                     | 2 / 636 (0.31%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hyperkalaemia                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 0 / 615 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypoglycaemia                                   |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 636 (0.16%) | 0 / 34 (0.00%) | 2 / 615 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Pembrolizumab      | Pembrolizumab<br>Second Course | Chemotherapy (SOC<br>Treatment) |
|---|--------------------|--------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events |                    |                                |                                 |
| subjects affected / exposed                           | 535 / 636 (84.12%) | 21 / 34 (61.76%)               | 577 / 615 (93.82%)              |
| Vascular disorders                                    |                    |                                |                                 |
| Hypertension  |                    |                                |                                 |
| subjects affected / exposed                           | 41 / 636 (6.45%)   | 1 / 34 (2.94%)                 | 14 / 615 (2.28%)                |
| occurrences (all)                                     | 49                 | 1                              | 17                              |
| General disorders and administration site conditions  |                    |                                |                                 |
| Malaise   |                    |                                |                                 |
| subjects affected / exposed                           | 15 / 636 (2.36%)   | 1 / 34 (2.94%)                 | 32 / 615 (5.20%)                |
| occurrences (all)                                     | 15                 | 1                              | 49                              |
| Asthenia  |                    |                                |                                 |
| subjects affected / exposed                           | 69 / 636 (10.85%)  | 2 / 34 (5.88%)                 | 81 / 615 (13.17%)               |
| occurrences (all)                                     | 92                 | 3                              | 110                             |
| Chest pain  |                    |                                |                                 |
| subjects affected / exposed                           | 56 / 636 (8.81%)   | 1 / 34 (2.94%)                 | 43 / 615 (6.99%)                |
| occurrences (all)                                     | 61                 | 1                              | 52                              |
| Fatigue   |                    |                                |                                 |
| subjects affected / exposed                           | 101 / 636 (15.88%) | 0 / 34 (0.00%)                 | 129 / 615 (20.98%)              |
| occurrences (all)                                     | 129                | 0                              | 193                             |
| Pyrexia   |                    |                                |                                 |
| subjects affected / exposed                           | 64 / 636 (10.06%)  | 1 / 34 (2.94%)                 | 52 / 615 (8.46%)                |
| occurrences (all)                                     | 82                 | 1                              | 63                              |
| Oedema peripheral                                     |                    |                                |                                 |
| subjects affected / exposed                           | 32 / 636 (5.03%)   | 1 / 34 (2.94%)                 | 36 / 615 (5.85%)                |
| occurrences (all)                                     | 33                 | 1                              | 50                              |
| Respiratory, thoracic and mediastinal disorders       |                    |                                |                                 |
| Cough   |                    |                                |                                 |

|   |                           |                      |                          |
|---|---------------------------|----------------------|--------------------------|
| subjects affected / exposed<br>occurrences (all)  | 107 / 636 (16.82%)<br>128 | 2 / 34 (5.88%)<br>2  | 66 / 615 (10.73%)<br>72  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                | 105 / 636 (16.51%)<br>120 | 1 / 34 (2.94%)<br>1  | 72 / 615 (11.71%)<br>81  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)                             | 45 / 636 (7.08%)<br>62    | 3 / 34 (8.82%)<br>4  | 23 / 615 (3.74%)<br>25   |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)       | 34 / 636 (5.35%)<br>38    | 0 / 34 (0.00%)<br>0  | 45 / 615 (7.32%)<br>51   |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)      | 67 / 636 (10.53%)<br>71   | 4 / 34 (11.76%)<br>4 | 48 / 615 (7.80%)<br>49   |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                | 7 / 636 (1.10%)<br>7      | 0 / 34 (0.00%)<br>0  | 65 / 615 (10.57%)<br>144 |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)              | 6 / 636 (0.94%)<br>6      | 0 / 34 (0.00%)<br>0  | 89 / 615 (14.47%)<br>239 |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 62 / 636 (9.75%)<br>83    | 3 / 34 (8.82%)<br>3  | 57 / 615 (9.27%)<br>87   |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)      | 66 / 636 (10.38%)<br>89   | 3 / 34 (8.82%)<br>4  | 72 / 615 (11.71%)<br>97  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)        | 5 / 636 (0.79%)<br>7      | 1 / 34 (2.94%)<br>1  | 77 / 615 (12.52%)<br>228 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)    | 39 / 636 (6.13%)<br>46    | 2 / 34 (5.88%)<br>2  | 30 / 615 (4.88%)<br>35   |
| Nervous system disorders  |                           |                      |                          |

|                                      |                    |                |                    |
|--------------------------------------|--------------------|----------------|--------------------|
| Dizziness                            |                    |                |                    |
| subjects affected / exposed          | 25 / 636 (3.93%)   | 0 / 34 (0.00%) | 39 / 615 (6.34%)   |
| occurrences (all)                    | 28                 | 0              | 49                 |
| Headache                             |                    |                |                    |
| subjects affected / exposed          | 44 / 636 (6.92%)   | 2 / 34 (5.88%) | 51 / 615 (8.29%)   |
| occurrences (all)                    | 58                 | 2              | 62                 |
| Neuropathy peripheral                |                    |                |                    |
| subjects affected / exposed          | 5 / 636 (0.79%)    | 0 / 34 (0.00%) | 52 / 615 (8.46%)   |
| occurrences (all)                    | 6                  | 0              | 62                 |
| Peripheral sensory neuropathy        |                    |                |                    |
| subjects affected / exposed          | 4 / 636 (0.63%)    | 0 / 34 (0.00%) | 43 / 615 (6.99%)   |
| occurrences (all)                    | 5                  | 0              | 55                 |
| Blood and lymphatic system disorders |                    |                |                    |
| Thrombocytopenia                     |                    |                |                    |
| subjects affected / exposed          | 6 / 636 (0.94%)    | 0 / 34 (0.00%) | 59 / 615 (9.59%)   |
| occurrences (all)                    | 7                  | 0              | 86                 |
| Neutropenia                          |                    |                |                    |
| subjects affected / exposed          | 6 / 636 (0.94%)    | 0 / 34 (0.00%) | 85 / 615 (13.82%)  |
| occurrences (all)                    | 9                  | 0              | 177                |
| Anaemia                              |                    |                |                    |
| subjects affected / exposed          | 102 / 636 (16.04%) | 2 / 34 (5.88%) | 253 / 615 (41.14%) |
| occurrences (all)                    | 124                | 2              | 332                |
| Leukopenia                           |                    |                |                    |
| subjects affected / exposed          | 10 / 636 (1.57%)   | 1 / 34 (2.94%) | 35 / 615 (5.69%)   |
| occurrences (all)                    | 17                 | 1              | 63                 |
| Gastrointestinal disorders           |                    |                |                    |
| Diarrhoea                            |                    |                |                    |
| subjects affected / exposed          | 74 / 636 (11.64%)  | 3 / 34 (8.82%) | 78 / 615 (12.68%)  |
| occurrences (all)                    | 94                 | 5              | 107                |
| Constipation                         |                    |                |                    |
| subjects affected / exposed          | 78 / 636 (12.26%)  | 3 / 34 (8.82%) | 131 / 615 (21.30%) |
| occurrences (all)                    | 98                 | 3              | 168                |
| Nausea                               |                    |                |                    |
| subjects affected / exposed          | 73 / 636 (11.48%)  | 1 / 34 (2.94%) | 195 / 615 (31.71%) |
| occurrences (all)                    | 98                 | 1              | 407                |
| Vomiting                             |                    |                |                    |

|   |                   |                |                    |
|---|-------------------|----------------|--------------------|
| subjects affected / exposed                     | 50 / 636 (7.86%)  | 0 / 34 (0.00%) | 106 / 615 (17.24%) |
| occurrences (all)                               | 62                | 0              | 167                |
| Stomatitis                                      |                   |                |                    |
| subjects affected / exposed                     | 16 / 636 (2.52%)  | 0 / 34 (0.00%) | 33 / 615 (5.37%)   |
| occurrences (all)                               | 18                | 0              | 40                 |
| Skin and subcutaneous tissue disorders          |                   |                |                    |
| Alopecia  |                   |                |                    |
| subjects affected / exposed                     | 3 / 636 (0.47%)   | 0 / 34 (0.00%) | 138 / 615 (22.44%) |
| occurrences (all)                               | 4                 | 0              | 139                |
| Pruritus  |                   |                |                    |
| subjects affected / exposed                     | 67 / 636 (10.53%) | 2 / 34 (5.88%) | 22 / 615 (3.58%)   |
| occurrences (all)                               | 83                | 4              | 23                 |
| Rash  |                   |                |                    |
| subjects affected / exposed                     | 72 / 636 (11.32%) | 1 / 34 (2.94%) | 43 / 615 (6.99%)   |
| occurrences (all)                               | 82                | 4              | 52                 |
| Endocrine disorders                             |                   |                |                    |
| Hypothyroidism                                  |                   |                |                    |
| subjects affected / exposed                     | 76 / 636 (11.95%) | 3 / 34 (8.82%) | 10 / 615 (1.63%)   |
| occurrences (all)                               | 99                | 5              | 10                 |
| Hyperthyroidism                                 |                   |                |                    |
| subjects affected / exposed                     | 37 / 636 (5.82%)  | 1 / 34 (2.94%) | 4 / 615 (0.65%)    |
| occurrences (all)                               | 38                | 1              | 4                  |
| Musculoskeletal and connective tissue disorders |                   |                |                    |
| Pain in extremity                               |                   |                |                    |
| subjects affected / exposed                     | 31 / 636 (4.87%)  | 0 / 34 (0.00%) | 34 / 615 (5.53%)   |
| occurrences (all)                               | 36                | 0              | 40                 |
| Myalgia   |                   |                |                    |
| subjects affected / exposed                     | 32 / 636 (5.03%)  | 1 / 34 (2.94%) | 70 / 615 (11.38%)  |
| occurrences (all)                               | 37                | 1              | 135                |
| Back pain                                       |                   |                |                    |
| subjects affected / exposed                     | 61 / 636 (9.59%)  | 1 / 34 (2.94%) | 43 / 615 (6.99%)   |
| occurrences (all)                               | 70                | 1              | 51                 |
| Arthralgia                                      |                   |                |                    |
| subjects affected / exposed                     | 86 / 636 (13.52%) | 3 / 34 (8.82%) | 87 / 615 (14.15%)  |
| occurrences (all)                               | 109               | 3              | 162                |
| Infections and infestations                     |                   |                |                    |



|   |                           |                     |                           |
|---|---------------------------|---------------------|---------------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 46 / 636 (7.23%)<br>62    | 1 / 34 (2.94%)<br>1 | 32 / 615 (5.20%)<br>41    |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 39 / 636 (6.13%)<br>40    | 1 / 34 (2.94%)<br>1 | 30 / 615 (4.88%)<br>35    |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 26 / 636 (4.09%)<br>37    | 3 / 34 (8.82%)<br>4 | 21 / 615 (3.41%)<br>26    |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 30 / 636 (4.72%)<br>34    | 3 / 34 (8.82%)<br>4 | 23 / 615 (3.74%)<br>25    |
| Metabolism and nutrition disorders  |                           |                     |                           |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 21 / 636 (3.30%)<br>26    | 1 / 34 (2.94%)<br>1 | 32 / 615 (5.20%)<br>43    |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 108 / 636 (16.98%)<br>127 | 3 / 34 (8.82%)<br>3 | 134 / 615 (21.79%)<br>209 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 26 January 2016 | Updated Statistical Analysis Plan and Inclusion/Exclusion Criteria                         |
| 11 May 2017     | Updates to the primary, secondary, and exploratory objectives/hypothesis                   |
| 01 March 2018   | Expanded dose modification guidelines  |
| 20 April 2021   | Added language regarding the enrollment of participants in a pembrolizumab extension study |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported