



## Clinical trial results:

### An Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) Monotherapy in Subjects with Advanced or Metastatic Squamous Cell (Sq) Non-Small Cell Lung Cancer (NSCLC) who Have Received at Least One Prior Systemic Regimen for the Treatment of Stage IIIb/IV SqNSCLC Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2014-001285-10                      |
| Trial protocol           | HU SE DE FI DK PT ES AT GB IE GR RO |
| Global end of trial date | 27 August 2021                      |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v2 (current)      |
| This version publication date  | 02 November 2022  |
| First version publication date | 11 September 2022 |
| Version creation reason        |                   |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | CA209-171 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02409368 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bristol-Myers Squibb   |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170                                  |
| Public contact               | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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                       | 14 October 2021 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 27 August 2021  |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To determine the incidence of high-grade (CTCAE v4.0 Grades 3-4), treatment-related, select adverse events in subjects with advanced or metastatic SqNSCLC who progressed during or after at least 1 systemic therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 29 April 2015 |
| 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 | Austria: 9             |
| Country: Number of subjects enrolled | Denmark: 16            |
| Country: Number of subjects enrolled | Finland: 10            |
| Country: Number of subjects enrolled | Greece: 34             |
| Country: Number of subjects enrolled | Hungary: 51            |
| Country: Number of subjects enrolled | Ireland: 3             |
| Country: Number of subjects enrolled | Poland: 81             |
| Country: Number of subjects enrolled | Portugal: 28           |
| Country: Number of subjects enrolled | Romania: 79            |
| Country: Number of subjects enrolled | Russian Federation: 39 |
| Country: Number of subjects enrolled | Spain: 232             |
| Country: Number of subjects enrolled | Sweden: 18             |
| Country: Number of subjects enrolled | United Kingdom: 212    |
| Worldwide total number of subjects   | 812                    |
| EEA total number of subjects         | 561                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 331 |
| From 65 to 84 years                       | 480 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

1 subject was ECOG PS 3 and thus outside the scope of the protocol. There were 2 ECOG classification periods during this study. The first was used in Primary Endpoint analysis. The second was used in Baseline Characteristics, Secondary Endpoint, and AE analysis. 1 subject was lost from initial ECOG Classification but included at Study Completion.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |            |
|------------------|------------|
| <b>Arm title</b> | ECOG (PS0) |
|------------------|------------|

Arm description:

ECOG Performance Status 0 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Nivolumab       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

|                  |            |
|------------------|------------|
| <b>Arm title</b> | ECOG (PS1) |
|------------------|------------|

Arm description:

ECOG Performance Status 1 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Nivolumab       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | ECOG (PS 2) |
|------------------|-------------|

Arm description:

ECOG Performance Status 2 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Nivolumab       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

|   |                 |
|---|-----------------|
| <b>Arm title</b>  | ECOG (PS3)      |
| Arm description:  |                 |
| ECOG Performance Status 3 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |                 |
| Arm type  | Experimental    |
| Investigational medicinal product name  | Nivolumab       |
| Investigational medicinal product code  |                 |
| Other name  |                 |
| Pharmaceutical forms  | Infusion        |
| Routes of administration  | Intravenous use |

Dosage and administration details:

Nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks

| <b>Number of subjects in period 1</b>              | ECOG (PS0) | ECOG (PS1) | ECOG (PS 2) |
|--|------------|------------|-------------|
| Started  | 172        | 537        | 102         |
| Completed  | 0          | 0          | 0           |
| Not completed                                      | 172        | 537        | 102         |
| Adverse event, serious fatal                       | 1          | 5          | -           |
| Participant withdrew consent                       | 2          | 3          | 4           |
| Study drug toxicity                                | 17         | 42         | 7           |
| Other Reasons                                      | 5          | 26         | 2           |
| Maximum clinical benefit                           | 6          | 5          | -           |
| Participant no longer meets study criteria         | 3          | 8          | 3           |
| Adverse event unrelated to study drug              | 17         | 49         | 12          |
| Lost to follow-up                                  | 1          | 5          | -           |
| Poor/non-compliance                                | -          | 3          | 2           |
| Disease Progression                                | 113        | 382        | 70          |
| Participant request to discontinue study treatment | 6          | 6          | 2           |
| Administrative reason by sponsor                   | 1          | 3          | -           |

| <b>Number of subjects in period 1</b> | ECOG (PS3) |
|---------------------------------------|------------|
| Started                               | 1          |
| Completed                             | 0          |
| Not completed                         | 1          |
| Adverse event, serious fatal          | -          |
| Participant withdrew consent          | -          |
| Study drug toxicity                   | -          |

|  |   |
|--|---|
| Other Reasons                                      | - |
| Maximum clinical benefit                           | - |
| Participant no longer meets study criteria         | - |
| Adverse event unrelated to study drug              | - |
| Lost to follow-up                                  | - |
| Poor/non-compliance                                | - |
| Disease Progression                                | 1 |
| Participant request to discontinue study treatment | - |
| Administrative reason by sponsor                   | - |

## Baseline characteristics

### Reporting groups

|   |             |
|---|-------------|
| Reporting group title   | ECOG (PS0)  |
| Reporting group description:  |             |
| ECOG Performance Status 0 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |
| Reporting group title   | ECOG (PS1)  |
| Reporting group description:  |             |
| ECOG Performance Status 1 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |
| Reporting group title   | ECOG (PS 2) |
| Reporting group description:  |             |
| ECOG Performance Status 2 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |
| Reporting group title   | ECOG (PS3)  |
| Reporting group description:  |             |
| ECOG Performance Status 3 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |

| Reporting group values                    | ECOG (PS0) | ECOG (PS1) | ECOG (PS 2) |
|---|------------|------------|-------------|
| Number of subjects                        | 172        | 537        | 102         |
| Age categorical                           |            |            |             |
| Units: Subjects                           |            |            |             |
| Adults (18-64 years)                      | 83         | 217        | 31          |
| From 65-84 years                          | 89         | 320        | 70          |
| 85 years and over                         | 0          | 0          | 1           |
| Age Continuous                            |            |            |             |
| "999"=N/A                                 |            |            |             |
| Units: years                              |            |            |             |
| arithmetic mean                           | 63.6       | 66.1       | 67.9        |
| standard deviation                        | ± 8.28     | ± 8.27     | ± 7.29      |
| Sex: Female, Male                         |            |            |             |
| Units: Participants                       |            |            |             |
| Female                                    | 37         | 111        | 22          |
| Male                                      | 135        | 426        | 80          |
| Race (NIH/OMB)                            |            |            |             |
| Units: Subjects                           |            |            |             |
| American Indian or Alaska Native          | 0          | 0          | 0           |
| Asian                                     | 0          | 2          | 0           |
| Native Hawaiian or Other Pacific Islander | 0          | 0          | 0           |
| Black or African American                 | 0          | 3          | 0           |
| White                                     | 165        | 530        | 102         |
| More than one race                        | 0          | 0          | 0           |
| Unknown or Not Reported                   | 7          | 2          | 0           |
| Ethnicity (NIH/OMB)                       |            |            |             |
| Units: Subjects                           |            |            |             |
| Hispanic or Latino                        | 13         | 37         | 11          |
| Not Hispanic or Latino                    | 159        | 500        | 91          |
| Unknown or Not Reported                   | 0          | 0          | 0           |

| Reporting group values | ECOG (PS3) | Total |  |
|------------------------|------------|-------|--|
|------------------------|------------|-------|--|

|   |       |     |  |
|---|-------|-----|--|
| Number of subjects                        | 1     | 812 |  |
| Age categorical                           |       |     |  |
| Units: Subjects                           |       |     |  |
| Adults (18-64 years)                      | 0     | 331 |  |
| From 65-84 years                          | 1     | 480 |  |
| 85 years and over                         | 0     | 1   |  |
| Age Continuous                            |       |     |  |
| "999"=N/A                                 |       |     |  |
| Units: years                              |       |     |  |
| arithmetic mean                           | 71    |     |  |
| standard deviation                        | ± 999 | -   |  |
| Sex: Female, Male                         |       |     |  |
| Units: Participants                       |       |     |  |
| Female                                    | 1     | 171 |  |
| Male                                      | 0     | 641 |  |
| Race (NIH/OMB)                            |       |     |  |
| Units: Subjects                           |       |     |  |
| American Indian or Alaska Native          | 0     | 0   |  |
| Asian                                     | 0     | 2   |  |
| Native Hawaiian or Other Pacific Islander | 0     | 0   |  |
| Black or African American                 | 0     | 3   |  |
| White                                     | 1     | 798 |  |
| More than one race                        | 0     | 0   |  |
| Unknown or Not Reported                   | 0     | 9   |  |
| Ethnicity (NIH/OMB)                       |       |     |  |
| Units: Subjects                           |       |     |  |
| Hispanic or Latino                        | 0     | 61  |  |
| Not Hispanic or Latino                    | 1     | 751 |  |
| Unknown or Not Reported                   | 0     | 0   |  |



## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | ECOG (PS0)  |
| Reporting group description:  |             |
| ECOG Performance Status 0 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |
| Reporting group title   | ECOG (PS1)  |
| Reporting group description:  |             |
| ECOG Performance Status 1 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |
| Reporting group title   | ECOG (PS 2) |
| Reporting group description:  |             |
| ECOG Performance Status 2 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |
| Reporting group title   | ECOG (PS3)  |
| Reporting group description:  |             |
| ECOG Performance Status 3 nivolumab 3 mg/kg as a 60- minute IV infusion every 2 weeks |             |

### Primary: Number of Participants With High Grade (Grade 3, 4 and 5) Treatment Related Select Adverse Events

|   |   |
|---|---|
| End point title   | Number of Participants With High Grade (Grade 3, 4 and 5) Treatment Related Select Adverse Events <sup>[1][2]</sup> |
| End point description:  |   |
| The total number of participants with high grade treatment related select adverse events. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| From first dose to time of analysis of primary endpoint (approximately up to 34 months)   |   |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics were planned for this endpoint

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only summary statistics were planned for this endpoint

| End point values                    | ECOG (PS0)      | ECOG (PS1)      | ECOG (PS 2)     |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 172             | 537             | 102             |  |
| Units: Participants                 |                 |                 |                 |  |
| Skin                                | 2               | 7               | 0               |  |
| Gastrointestinal                    | 1               | 10              | 0               |  |
| Endocrine                           | 4               | 3               | 0               |  |
| Hepatic                             | 4               | 12              | 2               |  |
| Pulmonary                           | 2               | 6               | 0               |  |
| Renal                               | 0               | 3               | 1               |  |
| Hypersensitivity/ Infusion reaction | 0               | 0               | 0               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with High Grade Select Adverse Events

|                 |   |
|-----------------|---|
| End point title | Number of Participants with High Grade Select Adverse |
|-----------------|---|

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. Select AEs include Pulmonary toxicity, Gastrointestinal toxicity (diarrhea or colitis, Endocrinopathies, Hepatotoxicity (including asymptomatic LFT elevations), Renal toxicity, Skin toxicity, and Neurological toxicity.

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

End point timeframe:

From first dose up to 100 days post last dose (up to 76 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only summary statistics were planned for this endpoint

| End point values                    | ECOG (PS0)      | ECOG (PS1)      | ECOG (PS 2)     |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 172             | 537             | 102             |  |
| Units: Participants                 |                 |                 |                 |  |
| Skin                                | 2               | 7               | 0               |  |
| Gastrointestinal                    | 1               | 11              | 0               |  |
| Endocrine                           | 5               | 4               | 0               |  |
| Hepatic                             | 6               | 19              | 3               |  |
| Pulmonary                           | 3               | 9               | 1               |  |
| Renal                               | 0               | 7               | 1               |  |
| Hypersensitivity/ Infusion reaction | 0               | 0               | 1               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median Time to Onset of Any Grade Select Adverse Events

|                 |  |
|-----------------|--|
| End point title | Median Time to Onset of Any Grade Select Adverse Events <sup>[4]</sup> |
|-----------------|--|

End point description:

Median Time to onset of any grade select adverse events reported up to 100 days after last doseMedian Time to onset of any grade select adverse events reported up to 100 days after last dose. An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. Select AEs include Pulmonary toxicity, Gastrointestinal toxicity (diarrhea or colitis, Endocrinopathies, Hepatotoxicity (including asymptomatic LFT elevations), Renal toxicity, Skin toxicity, and Neurological toxicity.

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

End point timeframe:

From first dose up to 100 days post last dose (up to approximately 65 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only summary statistics were planned for this endpoint

| End point values                   | ECOG (PS0)           | ECOG (PS1)           | ECOG (PS 2)         |  |
|------------------------------------|----------------------|----------------------|---------------------|--|
| Subject group type                 | Reporting group      | Reporting group      | Reporting group     |  |
| Number of subjects analysed        | 172                  | 537                  | 102                 |  |
| Units: Weeks                       |                      |                      |                     |  |
| median (full range (min-max))      |                      |                      |                     |  |
| Endocrine                          | 12.79 (4.0 to 121.6) | 10.14 (1.9 to 165.1) | 19.86 (6.1 to 55.4) |  |
| Gastrointestinal                   | 11.71 (0.1 to 88.0)  | 8.86 (0.1 to 228.1)  | 6.00 (0.3 to 64.3)  |  |
| Hepatic                            | 26.64 (1.4 to 234.1) | 11.43 (2.0 to 90.1)  | 8.14 (2.0 to 88.1)  |  |
| Pulmonary                          | 33.43 (7.4 to 169.4) | 11.50 (0.6 to 166.0) | 3.93 (0.1 to 26.3)  |  |
| Renal                              | 28.86 (4.1 to 129.9) | 22.71 (0.1 to 246.0) | 10.29 (1.4 to 52.9) |  |
| Skin                               | 12.14 (0.1 to 92.1)  | 7.86 (0.1 to 200.1)  | 14.71 (2.1 to 81.7) |  |
| Hypersensitivity/Infusion Reaction | 1.93 (1.7 to 2.1)    | 2.21 (0.3 to 20.3)   | 2.14 (2.1 to 28.6)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Time to Resolution of any Grade Select Adverse Events

|                 |   |
|-----------------|---|
| End point title | Median Time to Resolution of any Grade Select Adverse |
|-----------------|---|

End point description:

Median time to resolution of any grade select adverse events reported up to 100 days after last dose. An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. Select AEs include Pulmonary toxicity, Gastrointestinal toxicity (diarrhea or colitis, Endocrinopathies, Hepatotoxicity (including asymptomatic LFT elevations), Renal toxicity, Skin toxicity, and Neurological toxicity. "99999"=N/A

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

End point timeframe:

From first dose to up to 100 days post last dose (up to approximately 45 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only summary statistics were planned for this endpoint

| End point values                 | ECOG (PS0)              | ECOG (PS1)              | ECOG (PS 2)           |  |
|----------------------------------|-------------------------|-------------------------|-----------------------|--|
| Subject group type               | Reporting group         | Reporting group         | Reporting group       |  |
| Number of subjects analysed      | 172                     | 537                     | 102                   |  |
| Units: Weeks                     |                         |                         |                       |  |
| median (confidence interval 95%) |                         |                         |                       |  |
| Endocrine                        | 99999 (109.00 to 99999) | 169.43 (17.86 to 99999) | 99999 (6.14 to 99999) |  |
| Gastrointestinal                 | 2.86 (0.43 to 5.14)     | 2.00 (1.00 to 3.00)     | 2.00 (0.43 to 5.71)   |  |
| Hepatic                          | 4.57 (2.57 to 6.14)     | 7.71 (4.86 to 17.14)    | 3.57 (2.14 to 8.14)   |  |

|                                    |                        |                       |                       |  |
|------------------------------------|------------------------|-----------------------|-----------------------|--|
| Pulmonary                          | 3.00 (1.43 to 99999)   | 4.29 (2.14 to 6.00)   | 2.29 (1.00 to 99999)  |  |
| Renal                              | 10.14 (2.14 to 99999)  | 6.14 (2.29 to 25.14)  | 59.14 (0.57 to 59.14) |  |
| Skin                               | 99999 (13.57 to 99999) | 15.43 (8.71 to 52.86) | 5.71 (2.00 to 99999)  |  |
| Hypersensitivity/Infusion Reaction | 1.14 (0.14 to 2.14)    | 0.14 (0.14 to 4.43)   | 0.14 (0.14 to 0.71)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Overall Survival <sup>[6]</sup> |
|-----------------|---------------------------------|

End point description:

Overall Survival (OS) is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on treatment and every 3 months via in-person or phone contact after subjects discontinue the study drug.

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

End point timeframe:

From the first dosing up to the date of death (up to approximately 76 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only summary statistics were planned for this endpoint

| End point values                 | ECOG (PS0)         | ECOG (PS1)         | ECOG (PS 2)      |  |
|----------------------------------|--------------------|--------------------|------------------|--|
| Subject group type               | Reporting group    | Reporting group    | Reporting group  |  |
| Number of subjects analysed      | 172                | 537                | 102              |  |
| Units: Months                    |                    |                    |                  |  |
| median (confidence interval 95%) | 12.1 (9.9 to 13.4) | 10.3 (9.3 to 11.3) | 5.2 (3.0 to 7.6) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR)

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) <sup>[7]</sup> |
|-----------------|--|

End point description:

ORR is defined as the percentage of subjects with a best overall response (BOR) of confirmed CR or PR with respect to all treated participants. ORR as assessed by the investigator will be reported.

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

End point timeframe:

From first dose up to last dose (up to approximately 76 months)

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Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Only summary statistics were planned for this endpoint

| <b>End point values</b>          | ECOG (PS0)        | ECOG (PS1)         | ECOG (PS 2)      |  |
|----------------------------------|-------------------|--------------------|------------------|--|
| Subject group type               | Reporting group   | Reporting group    | Reporting group  |  |
| Number of subjects analysed      | 150               | 456                | 64               |  |
| Units: Percentage                |                   |                    |                  |  |
| number (confidence interval 95%) | 8.0 (4.2 to 13.6) | 11.0 (8.2 to 14.2) | 1.6 (0.0 to 8.4) |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs are reported from start of the treatment until the end of treatment + 100 days

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | ECOG Performance Status 0 |
|-----------------------|---------------------------|

Reporting group description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | ECOG Performance Status 2 |
|-----------------------|---------------------------|

Reporting group description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks

|                       |                           |
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| Reporting group title | ECOG Performance Status 3 |
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Reporting group description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks

|                       |                           |
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| Reporting group title | ECOG Performance Status 1 |
|-----------------------|---------------------------|

Reporting group description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks

| Serious adverse events  | ECOG Performance Status 0 | ECOG Performance Status 2 | ECOG Performance Status 3 |
|---|---------------------------|---------------------------|---------------------------|
| Total subjects affected by serious adverse events                   |                           |                           |                           |
| subjects affected / exposed   | 115 / 172 (66.86%)        | 84 / 102 (82.35%)         | 1 / 1 (100.00%)           |
| number of deaths (all causes)                                       | 131                       | 90                        | 1                         |
| number of deaths resulting from adverse events                      |                           |                           |                           |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                           |                           |
| Bladder cancer  |                           |                           |                           |
| subjects affected / exposed   | 0 / 172 (0.00%)           | 0 / 102 (0.00%)           | 0 / 1 (0.00%)             |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0                     |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0                     |
| Adenocarcinoma of colon   |                           |                           |                           |
| subjects affected / exposed   | 0 / 172 (0.00%)           | 0 / 102 (0.00%)           | 0 / 1 (0.00%)             |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0                     |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0                     |
| Bladder neoplasm  |                           |                           |                           |

|   |                   |                   |               |
|---|-------------------|-------------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)   | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0         |
| Brain cancer metastatic                         |                   |                   |               |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)   | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0         |
| Cancer pain                                     |                   |                   |               |
| subjects affected / exposed                     | 3 / 172 (1.74%)   | 1 / 102 (0.98%)   | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0         |
| Colon cancer                                    |                   |                   |               |
| subjects affected / exposed                     | 1 / 172 (0.58%)   | 0 / 102 (0.00%)   | 0 / 1 (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         |
| Follicular thyroid cancer                       |                   |                   |               |
| subjects affected / exposed                     | 1 / 172 (0.58%)   | 0 / 102 (0.00%)   | 0 / 1 (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         |
| Malignant neoplasm progression                  |                   |                   |               |
| subjects affected / exposed                     | 59 / 172 (34.30%) | 58 / 102 (56.86%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 60            | 0 / 59            | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 57            | 0 / 56            | 0 / 0         |
| Lung neoplasm malignant                         |                   |                   |               |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 1 / 102 (0.98%)   | 0 / 1 (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         |
| Metastases to central nervous system            |                   |                   |               |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)   | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0         |
| Metastases to lymph nodes                       |                   |                   |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Non-small cell lung cancer metastatic           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Oncologic complication                          |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pancreatic carcinoma                            |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Small intestine adenocarcinoma                  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 pain                                     |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Tumour compression                              |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 associated fever                         |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Vascular disorders                              |                 |                 |               |
| Deep vein thrombosis                            |                 |                 |               |



|  |                 |                 |               |
|--|-----------------|-----------------|---------------|
| subjects affected / exposed                          | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Embolism   |                 |                 |               |
| subjects affected / exposed                          | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypertension   |                 |                 |               |
| subjects affected / exposed                          | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Peripheral ischaemia                                 |                 |                 |               |
| subjects affected / exposed                          | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypotension  |                 |                 |               |
| subjects affected / exposed                          | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Superior vena cava occlusion                         |                 |                 |               |
| subjects affected / exposed                          | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Superior vena cava syndrome                          |                 |                 |               |
| subjects affected / exposed                          | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Venous thrombosis limb                               |                 |                 |               |
| subjects affected / exposed                          | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| General disorders and administration site conditions |                 |                 |               |
| Asthenia   |                 |                 |               |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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           |
| Death   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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           |
| Fatigue   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| General physical health deterioration           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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           |
| Hernia obstructive                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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           |
| Pain  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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           |
| Oedema peripheral                               |                 |                 |                 |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pyrexia   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Sudden cardiac death                            |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Sudden death                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Systemic inflammatory response syndrome         |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 system disorders                         |                 |                 |               |
| Drug hypersensitivity                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Respiratory, thoracic and mediastinal disorders |                 |                 |               |
| Aspiration                                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Acute respiratory failure                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| Asthma  |                 |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%)  | 0 / 1 (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           |
| Atelectasis                                     |                 |                  |                 |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 0 / 102 (0.00%)  | 0 / 1 (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           |
| Bronchial obstruction                           |                 |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                  |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 5 / 102 (4.90%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Bronchopneumopathy                              |                 |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Dyspnoea  |                 |                  |                 |
| subjects affected / exposed                     | 9 / 172 (5.23%) | 10 / 102 (9.80%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 1 / 10          | 0 / 11           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            | 0 / 0           |
| Epistaxis                                       |                 |                  |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%)  | 0 / 1 (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           |
| Haemoptysis                                     |                 |                  |                 |
| subjects affected / exposed                     | 7 / 172 (4.07%) | 3 / 102 (2.94%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 1 / 7           | 0 / 4            | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 3           | 0 / 2            | 0 / 0           |
| Hypoxia   |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Immune-mediated lung disease                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Interstitial lung disease                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung consolidation                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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           |
| Oesophagobronchial fistula                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 3 / 172 (1.74%) | 2 / 102 (1.96%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 4 / 172 (2.33%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 3 / 5           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax                                    |                 |                 |                 |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Pulmonary embolism                              |                 |                 |               |
| subjects affected / exposed                     | 3 / 172 (1.74%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Pulmonary haemorrhage                           |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| Respiratory tract haemorrhage                   |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Respiratory failure                             |                 |                 |               |
| subjects affected / exposed                     | 3 / 172 (1.74%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0         |
| Tracheal stenosis                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Psychiatric disorders                           |                 |                 |               |
| Agitation                                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Confusional state                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Delirium  |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Mania   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Investigations                                  |                 |                 |               |
| Alanine aminotransferase increased              |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Gamma-glutamyltransferase increased             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Aspartate aminotransferase increased            |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Liver function test increased                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Injury, poisoning and procedural complications  |                 |                 |               |
| Accidental overdose                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Concussion                                      |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Fall  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Femur fracture                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Foreign body in gastrointestinal tract          |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hip fracture                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Humerus fracture                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Infusion related reaction                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Overdose  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Radiation oesophagitis                          |                 |                 |               |



|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Skull fractured base                            |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Rib fracture                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Spinal compression fracture                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Splenic rupture                                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 haematoma                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Tracheal obstruction                            |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Upper limb fracture                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Congenital, familial and genetic disorders      |                 |                 |               |
| Tracheo-oesophageal fistula                     |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac disorders                               |                 |                 |               |
| Atrial fibrillation                             |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Atrial flutter                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac arrest                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac failure                                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 congestive                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac tamponade                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Cardio-respiratory arrest                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| Cardiomegaly                                    |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Intracardiac thrombus                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Left ventricular failure                        |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Mitral valve prolapse                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Myocardial infarction                           |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0         |
| Pericarditis                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pericardial effusion                            |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Sinus tachycardia                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Supraventricular extrasystoles                  |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Nervous system disorders                        |                 |                 |               |
| Cerebral haemorrhage                            |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Brain oedema                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cerebral infarction                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cerebrovascular accident                        |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Coma  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Epilepsy  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Intracranial pressure increased                 |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 2 / 172 (1.16%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Lacunar infarction                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Loss of consciousness                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Monoparesis                                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Motor dysfunction                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Neuropathy peripheral                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Peripheral sensory neuropathy                   |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Spinal cord compression                         |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Status epilepticus                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Syncope   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 3 / 102 (2.94%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Tremor  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Transient ischaemic attack                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Blood and lymphatic system disorders            |                 |                 |               |
| Anaemia   |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Thrombocytopenia                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastrointestinal disorders                      |                 |                 |               |
| Abdominal pain                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Abdominal pain upper                            |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Anal fissure                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Ascites   |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Autoimmune colitis                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Colitis   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Colitis microscopic                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Constipation                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Diarrhoea                                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Dysphagia                                       |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Gastric ulcer                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastritis                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastrointestinal disorder                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastroesophageal reflux disease                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Immune-mediated enterocolitis                   |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Inguinal hernia                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Intestinal obstruction                          |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Large intestinal obstruction                    |                 |                 |               |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal rupture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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           |
| Oesophageal stenosis                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Autoimmune hepatitis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 2 / 102 (1.96%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Biliary tract disorder                          |                 |                 |                 |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cholangitis                                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Drug-induced liver injury                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Hepatic failure                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hyperbilirubinaemia                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Immune-mediated hepatitis                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Jaundice  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Jaundice cholestatic                            |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Liver injury                                    |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Skin and subcutaneous tissue disorders          |                 |                 |               |
| Angioedema                                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Rash macular                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Renal and urinary disorders                     |                 |                 |               |
| Acute kidney injury                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Calculus urinary                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Leukocyturia                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Nephrolithiasis                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Renal failure                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Urinary retention                               |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Urinary tract obstruction                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Endocrine disorders                             |                 |                 |               |
| Adrenal insufficiency                           |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Hypercalcaemia of malignancy                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hyperthyroidism                                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Thyroiditis                                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypothyroidism                                  |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Musculoskeletal and connective tissue disorders |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Arthralgia                                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Arthritis                                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Back pain                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Bone pain                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Muscular weakness                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Musculoskeletal chest pain                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Osteonecrosis                                   |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Patellofemoral pain syndrome                    |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pathological fracture                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Spinal pain                                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Infections and infestations                     |                 |                 |               |
| Abscess   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Bacteraemia                                     |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Bacterial diarrhoea                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Anal abscess                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Bacterial infection                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Bronchitis                                      |                 |                 |               |
| subjects affected / exposed                     | 4 / 172 (2.33%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Bronchitis bacterial                            |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| COVID-19  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| COVID-19 pneumonia                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Clostridium colitis                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cellulitis                                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cystitis  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| H1N1 influenza                                  |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                                   | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Infection   |                 |                 |               |
| subjects affected / exposed                                   | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |               |
| subjects affected / exposed                                   | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Lower respiratory tract infection                             |                 |                 |               |
| subjects affected / exposed                                   | 5 / 172 (2.91%) | 5 / 102 (4.90%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 6           | 0 / 5           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Mediastinitis   |                 |                 |               |
| subjects affected / exposed                                   | 0 / 172 (0.00%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Meningitis aseptic  |                 |                 |               |
| subjects affected / exposed                                   | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Neutropenic sepsis  |                 |                 |               |
| subjects affected / exposed                                   | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Parainfluenzae virus infection                                |                 |                 |               |
| subjects affected / exposed                                   | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Pneumonia bacterial   |                 |                 |               |



|   |                   |                  |                 |
|---|-------------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| Pneumonia                                       |                   |                  |                 |
| subjects affected / exposed                     | 20 / 172 (11.63%) | 10 / 102 (9.80%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 0 / 22            | 0 / 11           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2            | 0 / 0           |
| Pneumonia cytomegaloviral                       |                   |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| Pneumonia fungal                                |                   |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| Pneumonia pneumococcal                          |                   |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| Pulmonary sepsis                                |                   |                  |                 |
| subjects affected / exposed                     | 1 / 172 (0.58%)   | 0 / 102 (0.00%)  | 0 / 1 (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           |
| Pulmonary tuberculosis                          |                   |                  |                 |
| subjects affected / exposed                     | 0 / 172 (0.00%)   | 0 / 102 (0.00%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| Respiratory tract infection                     |                   |                  |                 |
| subjects affected / exposed                     | 11 / 172 (6.40%)  | 3 / 102 (2.94%)  | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 2 / 14            | 0 / 8            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| Sepsis  |                   |                  |                 |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 3 / 172 (1.74%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0         |
| Septic shock                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Staphylococcal infection                        |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Streptococcal infection                         |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Tracheobronchitis                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Upper respiratory tract infection               |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Urinary tract infection                         |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 1 / 102 (0.98%) | 0 / 1 (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         |
| Vulval abscess                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Metabolism and nutrition disorders              |                 |                 |               |
| Decreased appetite                              |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cachexia  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Dehydration                                     |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 1 / 102 (0.98%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Diabetes mellitus                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypercalcaemia                                  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 3 / 102 (2.94%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Diabetic metabolic decompensation               |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hyperglycaemia                                  |                 |                 |               |
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Hypoalbuminaemia                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hyperkalaemia                                   |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 172 (0.58%) | 0 / 102 (0.00%) | 0 / 1 (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         |
| Hypoglycaemia                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypokalaemia                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 172 (0.00%) | 0 / 102 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hyponatraemia                                   |                 |                 |               |
| subjects affected / exposed                     | 2 / 172 (1.16%) | 2 / 102 (1.96%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |

| <b>Serious adverse events</b>                                       | ECOG Performance Status 1 |  |  |
|---|---------------------------|--|--|
| Total subjects affected by serious adverse events                   |                           |  |  |
| subjects affected / exposed   | 375 / 537 (69.83%)        |  |  |
| number of deaths (all causes)                                       | 446                       |  |  |
| number of deaths resulting from adverse events                      |                           |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |  |  |
| Bladder cancer  |                           |  |  |
| subjects affected / exposed   | 2 / 537 (0.37%)           |  |  |
| occurrences causally related to treatment / all                     | 0 / 2                     |  |  |
| deaths causally related to treatment / all                          | 0 / 0                     |  |  |
| Adenocarcinoma of colon   |                           |  |  |
| subjects affected / exposed   | 1 / 537 (0.19%)           |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                     |  |  |
| deaths causally related to treatment / all                          | 0 / 0                     |  |  |
| Bladder neoplasm  |                           |  |  |
| subjects affected / exposed   | 1 / 537 (0.19%)           |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                     |  |  |
| deaths causally related to treatment / all                          | 0 / 0                     |  |  |

|   |                    |  |  |  |
|---|--------------------|--|--|--|
| Brain cancer metastatic                         |                    |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 1              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Cancer pain                                     |                    |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 2              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Colon cancer                                    |                    |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 0              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Follicular thyroid cancer                       |                    |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 0              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Malignant neoplasm progression                  |                    |  |  |  |
| subjects affected / exposed                     | 206 / 537 (38.36%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 210            |  |  |  |
| deaths causally related to treatment / all      | 0 / 198            |  |  |  |
| Lung neoplasm malignant                         |                    |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 1              |  |  |  |
| deaths causally related to treatment / all      | 0 / 1              |  |  |  |
| Metastases to central nervous system            |                    |  |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 3              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Metastases to lymph nodes                       |                    |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)    |  |  |  |
| occurrences causally related to treatment / all | 0 / 1              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Non-small cell lung cancer metastatic           |                    |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oncologic complication                          |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatic carcinoma                            |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Small intestine adenocarcinoma                  |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tumour pain                                     |                 |  |  |
| subjects affected / exposed                     | 5 / 537 (0.93%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tumour compression                              |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tumour associated fever                         |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Deep vein thrombosis                            |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Embolism  |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypertension   |                 |  |  |
| subjects affected / exposed                          | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Peripheral ischaemia                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypotension  |                 |  |  |
| subjects affected / exposed                          | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Superior vena cava occlusion                         |                 |  |  |
| subjects affected / exposed                          | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Superior vena cava syndrome                          |                 |  |  |
| subjects affected / exposed                          | 4 / 537 (0.74%) |  |  |
| occurrences causally related to treatment / all      | 0 / 6           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Venous thrombosis limb                               |                 |  |  |
| subjects affected / exposed                          | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest pain   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Death   |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Fatigue   |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| General physical health deterioration           |                 |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hernia obstructive                              |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Non-cardiac chest pain                          |                 |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pain  |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oedema peripheral                               |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyrexia   |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 8 / 537 (1.49%) |  |  |
| occurrences causally related to treatment / all | 1 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sudden cardiac death                            |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Sudden death                                    |                 |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%) |  |  |
| occurrences causally related to treatment / all | 1 / 4           |  |  |
| deaths causally related to treatment / all      | 1 / 4           |  |  |
| Systemic inflammatory response syndrome         |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune system disorders                         |                 |  |  |
| Drug hypersensitivity                           |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Aspiration                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Acute respiratory failure                       |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Asthma  |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| Atelectasis                                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bronchial obstruction                           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Chronic obstructive pulmonary disease           |                  |  |  |  |
| subjects affected / exposed                     | 7 / 537 (1.30%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bronchopneumopathy                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Dyspnoea  |                  |  |  |  |
| subjects affected / exposed                     | 28 / 537 (5.21%) |  |  |  |
| occurrences causally related to treatment / all | 4 / 31           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Epistaxis                                       |                  |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Haemoptysis                                     |                  |  |  |  |
| subjects affected / exposed                     | 11 / 537 (2.05%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 11           |  |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |  |
| Hypoxia   |                  |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Immune-mediated lung disease                    |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Interstitial lung disease                       |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lung consolidation                              |                  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophagobronchial fistula                      |                  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleural effusion                                |                  |  |  |
| subjects affected / exposed                     | 10 / 537 (1.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia aspiration                            |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pneumonitis                                     |                  |  |  |
| subjects affected / exposed                     | 15 / 537 (2.79%) |  |  |
| occurrences causally related to treatment / all | 14 / 16          |  |  |
| deaths causally related to treatment / all      | 2 / 2            |  |  |
| Pneumothorax                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pulmonary embolism                              |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 6 / 537 (1.12%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pulmonary haemorrhage                           |                  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Respiratory tract haemorrhage                   |                  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory failure                             |                  |  |  |
| subjects affected / exposed                     | 10 / 537 (1.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 12           |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Tracheal stenosis                               |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psychiatric disorders                           |                  |  |  |
| Agitation                                       |                  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Confusional state                               |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Delirium  |                  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mania   |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Investigations</b>                                 |                 |  |  |
| Alanine aminotransferase increased                    |                 |  |  |
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 1 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| Gamma-glutamyltransferase increased                   |                 |  |  |
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 1 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| Aspartate aminotransferase increased                  |                 |  |  |
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 1 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| Liver function test increased                         |                 |  |  |
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 1 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Injury, poisoning and procedural complications</b> |                 |  |  |
| Accidental overdose                                   |                 |  |  |
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| Concussion  |                 |  |  |
| subjects affected / exposed                           | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| Fall  |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femur fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Foreign body in gastrointestinal tract          |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hip fracture                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Humerus fracture                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infusion related reaction                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Overdose  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Radiation oesophagitis                          |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Skull fractured base                            |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Rib fracture                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal compression fracture                     |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Splenic rupture                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Tracheal obstruction                            |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper limb fracture                             |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Congenital, familial and genetic disorders      |                 |  |  |
| Tracheo-oesophageal fistula                     |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Atrial fibrillation                             |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Atrial flutter                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac arrest                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Cardiac failure                                 |                 |  |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure congestive                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac tamponade                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardio-respiratory arrest                       |                 |  |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 3           |  |  |  |
| Cardiomegaly                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Intracardiac thrombus                           |                 |  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Left ventricular failure                        |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mitral valve prolapse                           |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pericarditis                                    |                 |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pericardial effusion                            |                 |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Sinus tachycardia                               |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Supraventricular extrasystoles                  |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Cerebral haemorrhage                            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Brain oedema                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral infarction                             |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Coma  |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Epilepsy  |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intracranial pressure increased                 |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lacunar infarction                              |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Loss of consciousness                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Monoparesis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Motor dysfunction                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Neuropathy peripheral                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Peripheral sensory neuropathy                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Seizure   |                 |  |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Spinal cord compression                         |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Status epilepticus                              |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope   |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tremor  |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Anaemia   |                 |  |  |
| subjects affected / exposed                     | 6 / 537 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombocytopenia                                |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abdominal pain upper                            |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anal fissure                                    |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ascites   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Autoimmune colitis                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Colitis   |                 |  |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |  |
| occurrences causally related to treatment / all | 4 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Colitis microscopic                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Constipation                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diarrhoea                                       |                 |  |  |  |
| subjects affected / exposed                     | 7 / 537 (1.30%) |  |  |  |
| occurrences causally related to treatment / all | 4 / 7           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dysphagia                                       |                 |  |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastric ulcer                                   |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastritis                                       |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal disorder                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroesophageal reflux disease                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Immune-mediated enterocolitis                   |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Inguinal hernia                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Intestinal obstruction                          |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Large intestinal obstruction                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Nausea  |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oesophageal rupture                             |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oesophageal stenosis                            |                 |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Stomatitis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper gastrointestinal haemorrhage              |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Autoimmune hepatitis                            |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Biliary tract disorder                          |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholangitis                                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Drug-induced liver injury                       |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperbilirubinaemia                             |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune-mediated hepatitis                       |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Jaundice  |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Jaundice cholestatic                            |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Liver injury                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Angioedema                                      |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rash macular                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%) |  |  |
| occurrences causally related to treatment / all | 1 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Calculus urinary                                |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Leukocyturia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nephrolithiasis                                 |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%) |  |  |
| occurrences causally related to treatment / all | 1 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract obstruction                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocrine disorders                             |                 |  |  |
| Adrenal insufficiency                           |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypercalcaemia of malignancy                    |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperthyroidism                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypophysitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thyroiditis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypothyroidism                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Arthritis                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Back pain                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bone pain                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Muscular weakness                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Musculoskeletal chest pain                      |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Osteonecrosis                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pain in extremity                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Patellofemoral pain syndrome                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pathological fracture                           |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal pain                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Abscess   |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacteraemia                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial diarrhoea                             |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anal abscess                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial infection                             |                 |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Biliary sepsis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchitis                                      |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 9 / 537 (1.68%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 10          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchitis bacterial                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| COVID-19  |                 |  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| COVID-19 pneumonia                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Clostridium colitis                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cellulitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cystitis  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| H1N1 influenza                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infection                                       |                 |  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                                   | 2 / 537 (0.37%)  |  |  |  |
| occurrences causally related to treatment / all               | 0 / 2            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 1            |  |  |  |
| Infective exacerbation of chronic obstructive airways disease |                  |  |  |  |
| subjects affected / exposed                                   | 3 / 537 (0.56%)  |  |  |  |
| occurrences causally related to treatment / all               | 1 / 4            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0            |  |  |  |
| Lower respiratory tract infection                             |                  |  |  |  |
| subjects affected / exposed                                   | 21 / 537 (3.91%) |  |  |  |
| occurrences causally related to treatment / all               | 2 / 25           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 1            |  |  |  |
| Mediastinitis   |                  |  |  |  |
| subjects affected / exposed                                   | 0 / 537 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all               | 0 / 0            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0            |  |  |  |
| Meningitis aseptic  |                  |  |  |  |
| subjects affected / exposed                                   | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0            |  |  |  |
| Neutropenic sepsis  |                  |  |  |  |
| subjects affected / exposed                                   | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 1            |  |  |  |
| Parainfluenzae virus infection                                |                  |  |  |  |
| subjects affected / exposed                                   | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0            |  |  |  |
| Pneumonia bacterial   |                  |  |  |  |
| subjects affected / exposed                                   | 1 / 537 (0.19%)  |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1            |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0            |  |  |  |
| Pneumonia   |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 41 / 537 (7.64%) |  |  |
| occurrences causally related to treatment / all | 2 / 47           |  |  |
| deaths causally related to treatment / all      | 0 / 10           |  |  |
| Pneumonia cytomegaloviral                       |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia fungal                                |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia pneumococcal                          |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary sepsis                                |                  |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary tuberculosis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory tract infection                     |                  |  |  |
| subjects affected / exposed                     | 25 / 537 (4.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 26           |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Sepsis  |                  |  |  |
| subjects affected / exposed                     | 7 / 537 (1.30%)  |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Septic shock                                    |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Staphylococcal infection                        |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Streptococcal infection                         |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tracheobronchitis                               |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 5 / 537 (0.93%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vulval abscess                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Decreased appetite                              |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cachexia  |                 |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dehydration                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 537 (0.37%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diabetes mellitus                               |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypercalcaemia                                  |                  |  |  |
| subjects affected / exposed                     | 12 / 537 (2.23%) |  |  |
| occurrences causally related to treatment / all | 2 / 14           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diabetic metabolic decompensation               |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperglycaemia                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoalbuminaemia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperkalaemia                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 537 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoglycaemia                                   |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 537 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 537 (0.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | ECOG Performance Status 0 | ECOG Performance Status 2 | ECOG Performance Status 3 |
|---|---------------------------|---------------------------|---------------------------|
| Total subjects affected by non-serious adverse events |                           |                           |                           |
| subjects affected / exposed                           | 149 / 172 (86.63%)        | 86 / 102 (84.31%)         | 1 / 1 (100.00%)           |
| Vascular disorders                                    |                           |                           |                           |
| Hypertension  |                           |                           |                           |
| subjects affected / exposed                           | 12 / 172 (6.98%)          | 0 / 102 (0.00%)           | 0 / 1 (0.00%)             |
| occurrences (all)                                     | 15                        | 0                         | 0                         |
| General disorders and administration site conditions  |                           |                           |                           |
| Asthenia  |                           |                           |                           |
| subjects affected / exposed                           | 30 / 172 (17.44%)         | 15 / 102 (14.71%)         | 0 / 1 (0.00%)             |
| occurrences (all)                                     | 46                        | 19                        | 0                         |
| Fatigue   |                           |                           |                           |
| subjects affected / exposed                           | 40 / 172 (23.26%)         | 25 / 102 (24.51%)         | 1 / 1 (100.00%)           |
| occurrences (all)                                     | 48                        | 32                        | 1                         |
| Chest pain  |                           |                           |                           |
| subjects affected / exposed                           | 10 / 172 (5.81%)          | 1 / 102 (0.98%)           | 0 / 1 (0.00%)             |
| occurrences (all)                                     | 11                        | 1                         | 0                         |
| Non-cardiac chest pain                                |                           |                           |                           |
| subjects affected / exposed                           | 6 / 172 (3.49%)           | 5 / 102 (4.90%)           | 0 / 1 (0.00%)             |
| occurrences (all)                                     | 6                         | 8                         | 0                         |
| Oedema peripheral                                     |                           |                           |                           |

|   |                   |                   |                 |
|---|-------------------|-------------------|-----------------|
| subjects affected / exposed                     | 7 / 172 (4.07%)   | 14 / 102 (13.73%) | 1 / 1 (100.00%) |
| occurrences (all)                               | 8                 | 16                | 1               |
| Pyrexia   |                   |                   |                 |
| subjects affected / exposed                     | 9 / 172 (5.23%)   | 8 / 102 (7.84%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 11                | 10                | 0               |
| Influenza like illness                          |                   |                   |                 |
| subjects affected / exposed                     | 3 / 172 (1.74%)   | 2 / 102 (1.96%)   | 1 / 1 (100.00%) |
| occurrences (all)                               | 4                 | 2                 | 3               |
| Peripheral swelling                             |                   |                   |                 |
| subjects affected / exposed                     | 2 / 172 (1.16%)   | 2 / 102 (1.96%)   | 1 / 1 (100.00%) |
| occurrences (all)                               | 2                 | 2                 | 1               |
| Respiratory, thoracic and mediastinal disorders |                   |                   |                 |
| Cough   |                   |                   |                 |
| subjects affected / exposed                     | 44 / 172 (25.58%) | 19 / 102 (18.63%) | 0 / 1 (0.00%)   |
| occurrences (all)                               | 54                | 23                | 0               |
| Dyspnoea  |                   |                   |                 |
| subjects affected / exposed                     | 44 / 172 (25.58%) | 28 / 102 (27.45%) | 1 / 1 (100.00%) |
| occurrences (all)                               | 61                | 31                | 1               |
| Haemoptysis                                     |                   |                   |                 |
| subjects affected / exposed                     | 11 / 172 (6.40%)  | 10 / 102 (9.80%)  | 0 / 1 (0.00%)   |
| occurrences (all)                               | 12                | 12                | 0               |
| Pneumonitis                                     |                   |                   |                 |
| subjects affected / exposed                     | 10 / 172 (5.81%)  | 2 / 102 (1.96%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 11                | 2                 | 0               |
| Productive cough                                |                   |                   |                 |
| subjects affected / exposed                     | 3 / 172 (1.74%)   | 6 / 102 (5.88%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 3                 | 7                 | 0               |
| Pleural effusion                                |                   |                   |                 |
| subjects affected / exposed                     | 2 / 172 (1.16%)   | 1 / 102 (0.98%)   | 1 / 1 (100.00%) |
| occurrences (all)                               | 2                 | 1                 | 1               |
| Psychiatric disorders                           |                   |                   |                 |
| Anxiety   |                   |                   |                 |
| subjects affected / exposed                     | 9 / 172 (5.23%)   | 1 / 102 (0.98%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 9                 | 1                 | 0               |
| Investigations                                  |                   |                   |                 |

|                                      |                   |                   |                 |
|--------------------------------------|-------------------|-------------------|-----------------|
| Aspartate aminotransferase increased |                   |                   |                 |
| subjects affected / exposed          | 15 / 172 (8.72%)  | 5 / 102 (4.90%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 23                | 5                 | 0               |
| Alanine aminotransferase increased   |                   |                   |                 |
| subjects affected / exposed          | 12 / 172 (6.98%)  | 5 / 102 (4.90%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 20                | 5                 | 0               |
| Blood creatinine increased           |                   |                   |                 |
| subjects affected / exposed          | 9 / 172 (5.23%)   | 5 / 102 (4.90%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 13                | 5                 | 0               |
| Weight decreased                     |                   |                   |                 |
| subjects affected / exposed          | 8 / 172 (4.65%)   | 7 / 102 (6.86%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 8                 | 7                 | 0               |
| Nervous system disorders             |                   |                   |                 |
| Dizziness                            |                   |                   |                 |
| subjects affected / exposed          | 3 / 172 (1.74%)   | 8 / 102 (7.84%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 3                 | 8                 | 0               |
| Headache                             |                   |                   |                 |
| subjects affected / exposed          | 10 / 172 (5.81%)  | 3 / 102 (2.94%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 16                | 3                 | 0               |
| Seizure                              |                   |                   |                 |
| subjects affected / exposed          | 0 / 172 (0.00%)   | 0 / 102 (0.00%)   | 1 / 1 (100.00%) |
| occurrences (all)                    | 0                 | 0                 | 1               |
| Blood and lymphatic system disorders |                   |                   |                 |
| Anaemia                              |                   |                   |                 |
| subjects affected / exposed          | 23 / 172 (13.37%) | 21 / 102 (20.59%) | 1 / 1 (100.00%) |
| occurrences (all)                    | 25                | 35                | 1               |
| Eye disorders                        |                   |                   |                 |
| Lacrimation increased                |                   |                   |                 |
| subjects affected / exposed          | 0 / 172 (0.00%)   | 0 / 102 (0.00%)   | 1 / 1 (100.00%) |
| occurrences (all)                    | 0                 | 0                 | 1               |
| Gastrointestinal disorders           |                   |                   |                 |
| Abdominal pain                       |                   |                   |                 |
| subjects affected / exposed          | 2 / 172 (1.16%)   | 3 / 102 (2.94%)   | 0 / 1 (0.00%)   |
| occurrences (all)                    | 2                 | 4                 | 0               |
| Constipation                         |                   |                   |                 |

|   |                   |                   |                 |
|---|-------------------|-------------------|-----------------|
| subjects affected / exposed                     | 18 / 172 (10.47%) | 16 / 102 (15.69%) | 0 / 1 (0.00%)   |
| occurrences (all)                               | 18                | 18                | 0               |
| Diarrhoea                                       |                   |                   |                 |
| subjects affected / exposed                     | 26 / 172 (15.12%) | 16 / 102 (15.69%) | 0 / 1 (0.00%)   |
| occurrences (all)                               | 46                | 27                | 0               |
| Nausea  |                   |                   |                 |
| subjects affected / exposed                     | 20 / 172 (11.63%) | 16 / 102 (15.69%) | 0 / 1 (0.00%)   |
| occurrences (all)                               | 27                | 20                | 0               |
| Stomatitis                                      |                   |                   |                 |
| subjects affected / exposed                     | 5 / 172 (2.91%)   | 7 / 102 (6.86%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 9                 | 7                 | 0               |
| Vomiting  |                   |                   |                 |
| subjects affected / exposed                     | 9 / 172 (5.23%)   | 9 / 102 (8.82%)   | 1 / 1 (100.00%) |
| occurrences (all)                               | 11                | 15                | 1               |
| Skin and subcutaneous tissue disorders          |                   |                   |                 |
| Dry skin  |                   |                   |                 |
| subjects affected / exposed                     | 7 / 172 (4.07%)   | 6 / 102 (5.88%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 8                 | 6                 | 0               |
| Pruritus  |                   |                   |                 |
| subjects affected / exposed                     | 9 / 172 (5.23%)   | 10 / 102 (9.80%)  | 0 / 1 (0.00%)   |
| occurrences (all)                               | 9                 | 12                | 0               |
| Rash  |                   |                   |                 |
| subjects affected / exposed                     | 10 / 172 (5.81%)  | 5 / 102 (4.90%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 12                | 5                 | 0               |
| Endocrine disorders                             |                   |                   |                 |
| Hyperthyroidism                                 |                   |                   |                 |
| subjects affected / exposed                     | 13 / 172 (7.56%)  | 1 / 102 (0.98%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 15                | 1                 | 0               |
| Hypothyroidism                                  |                   |                   |                 |
| subjects affected / exposed                     | 25 / 172 (14.53%) | 6 / 102 (5.88%)   | 0 / 1 (0.00%)   |
| occurrences (all)                               | 25                | 6                 | 0               |
| Musculoskeletal and connective tissue disorders |                   |                   |                 |
| Back pain                                       |                   |                   |                 |
| subjects affected / exposed                     | 11 / 172 (6.40%)  | 7 / 102 (6.86%)   | 1 / 1 (100.00%) |
| occurrences (all)                               | 15                | 8                 | 1               |
| Arthralgia                                      |                   |                   |                 |

|                                   |                   |                 |                 |
|-----------------------------------|-------------------|-----------------|-----------------|
| subjects affected / exposed       | 24 / 172 (13.95%) | 7 / 102 (6.86%) | 1 / 1 (100.00%) |
| occurrences (all)                 | 27                | 7               | 1               |
| Pain in extremity                 |                   |                 |                 |
| subjects affected / exposed       | 4 / 172 (2.33%)   | 6 / 102 (5.88%) | 1 / 1 (100.00%) |
| occurrences (all)                 | 4                 | 6               | 1               |
| Musculoskeletal chest pain        |                   |                 |                 |
| subjects affected / exposed       | 7 / 172 (4.07%)   | 7 / 102 (6.86%) | 0 / 1 (0.00%)   |
| occurrences (all)                 | 7                 | 8               | 0               |
| Groin pain                        |                   |                 |                 |
| subjects affected / exposed       | 0 / 172 (0.00%)   | 0 / 102 (0.00%) | 1 / 1 (100.00%) |
| occurrences (all)                 | 0                 | 0               | 1               |
| Infections and infestations       |                   |                 |                 |
| Lower respiratory tract infection |                   |                 |                 |
| subjects affected / exposed       | 18 / 172 (10.47%) | 7 / 102 (6.86%) | 0 / 1 (0.00%)   |
| occurrences (all)                 | 23                | 12              | 0               |
| Nasopharyngitis                   |                   |                 |                 |
| subjects affected / exposed       | 11 / 172 (6.40%)  | 1 / 102 (0.98%) | 0 / 1 (0.00%)   |
| occurrences (all)                 | 15                | 1               | 0               |
| Pneumonia                         |                   |                 |                 |
| subjects affected / exposed       | 11 / 172 (6.40%)  | 5 / 102 (4.90%) | 0 / 1 (0.00%)   |
| occurrences (all)                 | 12                | 6               | 0               |
| Respiratory tract infection       |                   |                 |                 |
| subjects affected / exposed       | 10 / 172 (5.81%)  | 6 / 102 (5.88%) | 0 / 1 (0.00%)   |
| occurrences (all)                 | 14                | 7               | 0               |
| Upper respiratory tract infection |                   |                 |                 |
| subjects affected / exposed       | 10 / 172 (5.81%)  | 2 / 102 (1.96%) | 0 / 1 (0.00%)   |
| occurrences (all)                 | 15                | 2               | 0               |
| Catheter site infection           |                   |                 |                 |
| subjects affected / exposed       | 0 / 172 (0.00%)   | 0 / 102 (0.00%) | 1 / 1 (100.00%) |
| occurrences (all)                 | 0                 | 0               | 1               |
| Oral candidiasis                  |                   |                 |                 |
| subjects affected / exposed       | 4 / 172 (2.33%)   | 3 / 102 (2.94%) | 1 / 1 (100.00%) |
| occurrences (all)                 | 5                 | 5               | 1               |
| Tooth infection                   |                   |                 |                 |
| subjects affected / exposed       | 2 / 172 (1.16%)   | 0 / 102 (0.00%) | 1 / 1 (100.00%) |
| occurrences (all)                 | 3                 | 0               | 1               |

|   |                         |                         |                      |
|---|-------------------------|-------------------------|----------------------|
| Oral fungal infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 172 (0.00%)<br>0    | 0 / 102 (0.00%)<br>0    | 1 / 1 (100.00%)<br>1 |
| Metabolism and nutrition disorders  |                         |                         |                      |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)    | 24 / 172 (13.95%)<br>31 | 24 / 102 (23.53%)<br>32 | 0 / 1 (0.00%)<br>0   |
| Hypercalcaemia<br>subjects affected / exposed<br>occurrences (all)        | 6 / 172 (3.49%)<br>12   | 6 / 102 (5.88%)<br>6    | 0 / 1 (0.00%)<br>0   |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)         | 7 / 172 (4.07%)<br>12   | 6 / 102 (5.88%)<br>7    | 0 / 1 (0.00%)<br>0   |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)       | 11 / 172 (6.40%)<br>28  | 5 / 102 (4.90%)<br>6    | 0 / 1 (0.00%)<br>0   |

|   |                              |  |  |
|---|------------------------------|--|--|
| <b>Non-serious adverse events</b>   | ECOG Performance<br>Status 1 |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 472 / 537 (87.90%)           |  |  |
| Vascular disorders  |                              |  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                        | 19 / 537 (3.54%)<br>31       |  |  |
| General disorders and administration<br>site conditions                                 |                              |  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                            | 131 / 537 (24.39%)<br>170    |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                             | 121 / 537 (22.53%)<br>160    |  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                          | 24 / 537 (4.47%)<br>25       |  |  |
| Non-cardiac chest pain  |                              |  |  |

|   |                    |  |  |
|---|--------------------|--|--|
| subjects affected / exposed                     | 34 / 537 (6.33%)   |  |  |
| occurrences (all)                               | 37                 |  |  |
| Oedema peripheral                               |                    |  |  |
| subjects affected / exposed                     | 30 / 537 (5.59%)   |  |  |
| occurrences (all)                               | 32                 |  |  |
| Pyrexia   |                    |  |  |
| subjects affected / exposed                     | 49 / 537 (9.12%)   |  |  |
| occurrences (all)                               | 59                 |  |  |
| Influenza like illness                          |                    |  |  |
| subjects affected / exposed                     | 4 / 537 (0.74%)    |  |  |
| occurrences (all)                               | 5                  |  |  |
| Peripheral swelling                             |                    |  |  |
| subjects affected / exposed                     | 8 / 537 (1.49%)    |  |  |
| occurrences (all)                               | 8                  |  |  |
| Respiratory, thoracic and mediastinal disorders |                    |  |  |
| Cough   |                    |  |  |
| subjects affected / exposed                     | 134 / 537 (24.95%) |  |  |
| occurrences (all)                               | 160                |  |  |
| Dyspnoea  |                    |  |  |
| subjects affected / exposed                     | 167 / 537 (31.10%) |  |  |
| occurrences (all)                               | 204                |  |  |
| Haemoptysis                                     |                    |  |  |
| subjects affected / exposed                     | 47 / 537 (8.75%)   |  |  |
| occurrences (all)                               | 59                 |  |  |
| Pneumonitis                                     |                    |  |  |
| subjects affected / exposed                     | 22 / 537 (4.10%)   |  |  |
| occurrences (all)                               | 26                 |  |  |
| Productive cough                                |                    |  |  |
| subjects affected / exposed                     | 26 / 537 (4.84%)   |  |  |
| occurrences (all)                               | 30                 |  |  |
| Pleural effusion                                |                    |  |  |
| subjects affected / exposed                     | 6 / 537 (1.12%)    |  |  |
| occurrences (all)                               | 6                  |  |  |
| Psychiatric disorders                           |                    |  |  |



|  |  |  |  |
|--|--|--|--|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)  | 12 / 537 (2.23%)<br>13   |  |  |
| Investigations<br>Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Weight decreased<br>subjects affected / exposed<br>occurrences (all) | 28 / 537 (5.21%)<br>40<br><br>30 / 537 (5.59%)<br>41<br><br>34 / 537 (6.33%)<br>55<br><br>42 / 537 (7.82%)<br>45 |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Seizure<br>subjects affected / exposed<br>occurrences (all)   | 28 / 537 (5.21%)<br>33<br><br>36 / 537 (6.70%)<br>42<br><br>2 / 537 (0.37%)<br>2                                 |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 97 / 537 (18.06%)<br>126   |  |  |
| Eye disorders<br>Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 537 (0.19%)<br>1   |  |  |
| Gastrointestinal disorders   |  |  |  |

|  |                           |  |  |
|--|---------------------------|--|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 28 / 537 (5.21%)<br>34    |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                       | 80 / 537 (14.90%)<br>88   |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 100 / 537 (18.62%)<br>164 |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 71 / 537 (13.22%)<br>85   |  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)   | 14 / 537 (2.61%)<br>19    |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 34 / 537 (6.33%)<br>45    |  |  |
| Skin and subcutaneous tissue disorders<br>Dry skin<br>subjects affected / exposed<br>occurrences (all) | 26 / 537 (4.84%)<br>27    |  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 58 / 537 (10.80%)<br>76   |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 39 / 537 (7.26%)<br>41    |  |  |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)             | 18 / 537 (3.35%)<br>19    |  |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                                     | 37 / 537 (6.89%)<br>40    |  |  |
| Musculoskeletal and connective tissue disorders  |                           |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| Back pain                         |                  |  |  |
| subjects affected / exposed       | 46 / 537 (8.57%) |  |  |
| occurrences (all)                 | 56               |  |  |
| Arthralgia                        |                  |  |  |
| subjects affected / exposed       | 52 / 537 (9.68%) |  |  |
| occurrences (all)                 | 63               |  |  |
| Pain in extremity                 |                  |  |  |
| subjects affected / exposed       | 25 / 537 (4.66%) |  |  |
| occurrences (all)                 | 28               |  |  |
| Musculoskeletal chest pain        |                  |  |  |
| subjects affected / exposed       | 24 / 537 (4.47%) |  |  |
| occurrences (all)                 | 26               |  |  |
| Groin pain                        |                  |  |  |
| subjects affected / exposed       | 2 / 537 (0.37%)  |  |  |
| occurrences (all)                 | 2                |  |  |
| Infections and infestations       |                  |  |  |
| Lower respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 51 / 537 (9.50%) |  |  |
| occurrences (all)                 | 73               |  |  |
| Nasopharyngitis                   |                  |  |  |
| subjects affected / exposed       | 15 / 537 (2.79%) |  |  |
| occurrences (all)                 | 21               |  |  |
| Pneumonia                         |                  |  |  |
| subjects affected / exposed       | 24 / 537 (4.47%) |  |  |
| occurrences (all)                 | 31               |  |  |
| Respiratory tract infection       |                  |  |  |
| subjects affected / exposed       | 37 / 537 (6.89%) |  |  |
| occurrences (all)                 | 45               |  |  |
| Upper respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 29 / 537 (5.40%) |  |  |
| occurrences (all)                 | 38               |  |  |
| Catheter site infection           |                  |  |  |
| subjects affected / exposed       | 0 / 537 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Oral candidiasis                  |                  |  |  |

|   |                           |  |  |
|---|---------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                          | 26 / 537 (4.84%)<br>33    |  |  |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 537 (0.19%)<br>1      |  |  |
| Oral fungal infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 537 (0.19%)<br>1      |  |  |
| Metabolism and nutrition disorders  |                           |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)    | 147 / 537 (27.37%)<br>173 |  |  |
| Hypercalcaemia<br>subjects affected / exposed<br>occurrences (all)        | 39 / 537 (7.26%)<br>50    |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)         | 20 / 537 (3.72%)<br>27    |  |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)       | 27 / 537 (5.03%)<br>43    |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 21 November 2014 | The inclusion criteria have been expanded and the exclusion criteria have been minimized in order to expand the subject population. The background section has also been updated to reflect the most recently available data. Expanded palliative local therapy. Randomization after 1 year to subjects who are still benefitting from treatment and achieved a partial or complete response to offer insight into the optimal treatment duration of nivolumab has been added. After 1 year of therapy, subjects will be randomized to continue nivolumab monotherapy (Cohort A) or discontinue therapy with the option of retreatment disease progression (Cohort B). The requirement to have a separate assessment plan for the subjects in the Performance Status 2 (PS2) subgroup has been eliminated. The EQ-5D has been removed. Lung Cancer Symptom Survey has also been eliminated from the subject follow up and decreased while on treatment. Initial tumor assessments have also been changed to occur at Week 8 instead of Week 6. The statistical section has been reformatted. The phrase "rate and frequency" has been changed to the term "incidence" throughout the protocol. The term "Adverse Events of Special Interest" has been changed to "Select Adverse Events." The Performance Status groups were renamed "Subgroup" (from "Cohort") to avoid confusion with the randomized cohorts. Treatment discontinuation criteria were moved from Section 3.5 to the newly created Section 4.6.5.1 to follow the nivolumab protocol structure. The requirement for electrocardiograms has been removed as these tests are not done within the nivolumab clinical development program any more. |
| 18 June 2015     | The sample size was reduced from 1800 to 950 (with 15% screening failure rate, 800 will be treated); second-line lung cancer patients will now be allowed to enroll in the study; and the randomization at one year into Cohort A and Cohort B has been removed.  |
| 26 October 2016  | Adjustment to PS 0-1 and PS 2 subgroup sample numbers. Changes to informed consent procedure for treatment beyond disease progression. Clarification of SAE reporting to within 100 days of discontinuation of drug. Clarification of LCSS and TFT assessments timepoints. Addition of CBC/ TFTs to off-treatment follow-up scheduled lab test. Addition that dose must be recalculated if weight on the day of dosing differs by > 10% from the weight used to calculate the dose.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported