



## Clinical trial results:

### Open label multicenter Phase I/II study of the safety and efficacy of PDR001

### administered to patients with advanced malignancies

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2014-003929-17       |
| Trial protocol           | DE NL FR ES HU NO IT |
| Global end of trial date | 21 July 2020         |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 06 August 2021 |
| First version publication date | 06 August 2021 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CPDR001X2101 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02081378 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novartis Pharma, AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,   |
| Public contact               | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.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                       | 21 July 2020 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 21 July 2020 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

Phase I :To estimate the recommended Phase II dose (RP2D) and/or the maximum tolerated dose (MTD) for spartalizumab

Phase II: To estimate the anti-tumor activity of spartalizumab

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/#/>

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 27 April 2015 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 7         |
| Country: Number of subjects enrolled | France: 15        |
| Country: Number of subjects enrolled | Germany: 13       |
| Country: Number of subjects enrolled | Hungary: 7        |
| Country: Number of subjects enrolled | Italy: 34         |
| Country: Number of subjects enrolled | Lebanon: 3        |
| Country: Number of subjects enrolled | Netherlands: 12   |
| Country: Number of subjects enrolled | Norway: 11        |
| Country: Number of subjects enrolled | Poland: 13        |
| Country: Number of subjects enrolled | Spain: 55         |
| Country: Number of subjects enrolled | Taiwan: 36        |
| Country: Number of subjects enrolled | Thailand: 16      |
| Country: Number of subjects enrolled | Turkey: 22        |
| Country: Number of subjects enrolled | United States: 75 |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 319 |
| EEA total number of subjects       | 160 |

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)                      | 202 |
| From 65 to 84 years                       | 114 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

58 patients were analyzed in Phase I and 261 patients were analyzed in Phase II of this study.

### Pre-assignment

Screening details:

The study planned to analyze about 58 patients in Phase I and about 120 patients in Phase II.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Period (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> | 1 mg/kg q2w |
|------------------|-------------|

Arm description:

Phase I Dose escalation cohort patients who took PDR001 1 mg/kg q2w

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Spartalizumab                    |
| Investigational medicinal product code | PDR001                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Spartalizumab was administered via iv infusion over 30 minutes (up to two hours, if clinically indicated) once every 2 weeks and the starting dose was 1 mg/kg

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 3 mg/kg q2w |
|------------------|-------------|

Arm description:

Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q2w

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Spartalizumab   |
| Investigational medicinal product code | PDR001  |
| Other name                             |   |
| Pharmaceutical forms                   | Powder for infusion, Powder for solution for infusion |
| Routes of administration               | Intravenous use                                       |

Dosage and administration details:

Spartalizumab was administered via iv infusion over 30 minutes (up to two hours, if clinically indicated) once every 2 weeks and the starting dose was 1 mg/kg

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 10mg/kg q2w |
|------------------|-------------|

Arm description:

Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Spartalizumab                    |
| Investigational medicinal product code | PDR001                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Spartalizumab was administered via iv infusion over 30 minutes (up to two hours, if clinically indicated) once every 2 weeks and the starting dose was 1 mg/kg

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 3 mg/kg q4w |
|------------------|-------------|

Arm description:

Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Spartalizumab                    |
| Investigational medicinal product code | PDR001                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Spartalizumab was administered via iv infusion over 30 minutes (up to two hours, if clinically indicated) once every 2 weeks and the starting dose was 1 mg/kg

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 5 mg/kg q4w |
|------------------|-------------|

Arm description:

Phase I Dose escalation cohort patients who took PRD001 5 mg/kg q4w

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Spartalizumab                    |
| Investigational medicinal product code | PDR001                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Spartalizumab was administered via iv infusion over 30 minutes (up to two hours, if clinically indicated) once every 2 weeks and the starting dose was 1 mg/kg

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | NSCLC 400mg/q4w |
|------------------|-----------------|

Arm description:

Phase II: non-small cell cancer patients who took PDR001 400 mg/q4w

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Spartalizumab                    |
| Investigational medicinal product code | PDR001                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Subjects were all treated with a flat dose of Spartalizumab 400 mg Q4W.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Melanoma 400mg/q4w |
|------------------|--------------------|

Arm description:

Phase II: Melanoma patients who took PDR001 400 mg/q4w

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Spartalizumab                    |
| Investigational medicinal product code | PDR001                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Subjects were all treated with a flat dose of Spartalizumab 400 mg Q4W.

|  |                                  |
|--|----------------------------------|
| <b>Arm title</b>   | TNBC 400mg/q4w                   |
| Arm description:   |                                  |
| Phase II: Triple negative breast cancer (TNBC) patients who took PDR001 400 mg/q4w   |                                  |
| Arm type   | Experimental                     |
| Investigational medicinal product name   | Spartalizumab                    |
| Investigational medicinal product code   | PDR001                           |
| Other name   |                                  |
| Pharmaceutical forms   | Powder for solution for infusion |
| Routes of administration   | Intravenous use                  |
| Dosage and administration details:   |                                  |
| Subjects were all treated with a flat dose of Spartalizumab 400 mg Q4W.              |                                  |
| <b>Arm title</b>   | NSCLC 300mg/q3w                  |
| Arm description:   |                                  |
| Phase II: non-small cell cancer patients who took PDR001 300 mg/q3w                  |                                  |
| Arm type   | Experimental                     |
| Investigational medicinal product name   | Spartalizumab                    |
| Investigational medicinal product code   | PDR001                           |
| Other name   |                                  |
| Pharmaceutical forms   | Powder for solution for infusion |
| Routes of administration   | Intravenous use                  |
| Dosage and administration details:   |                                  |
| Subjects were all treated with a flat dose of Spartalizumab 300 mg Q3W.              |                                  |
| <b>Arm title</b>   | ATC 400 mg/q4w                   |
| Arm description:   |                                  |
| Patients in Phase II with anaplastic thyroid cancer (ATC) who took PDR001 400 mg/q4w |                                  |
| Arm type   | Experimental                     |
| Investigational medicinal product name   | Spartalizumab                    |
| Investigational medicinal product code   | PDR001                           |
| Other name   |                                  |
| Pharmaceutical forms   | Powder for solution for infusion |
| Routes of administration   | Intravenous use                  |
| Dosage and administration details:   |                                  |
| Subjects were all treated with a flat dose of Spartalizumab 400 mg Q4W.              |                                  |

| <b>Number of subjects in period 1</b> | 1 mg/kg q2w | 3 mg/kg q2w | 10mg/kg q2w |
|---------------------------------------|-------------|-------------|-------------|
| Started                               | 16          | 15          | 11          |
| Completed                             | 0           | 0           | 0           |
| Not completed                         | 16          | 15          | 11          |
| Adverse event, serious fatal          | 1           | 1           | 1           |
| Physician decision                    | -           | 1           | -           |
| Adverse event, non-fatal              | 1           | -           | -           |
| Progressive Disease                   | 14          | 11          | 7           |
| Subject/Guardian Decision             | -           | 2           | 3           |

| <b>Number of subjects in period 1</b> | 3 mg/kg q4w | 5 mg/kg q4w | NSCLC 400mg/q4w |
|---------------------------------------|-------------|-------------|-----------------|
|---------------------------------------|-------------|-------------|-----------------|

|                              |   |    |    |
|------------------------------|---|----|----|
| Started                      | 6 | 10 | 59 |
| Completed                    | 0 | 0  | 0  |
| Not completed                | 6 | 10 | 59 |
| Adverse event, serious fatal | - | 1  | 4  |
| Physician decision           | - | -  | 7  |
| Adverse event, non-fatal     | - | -  | 2  |
| Progressive Disease          | 6 | 9  | 43 |
| Subject/Guardian Decision    | - | -  | 3  |

| <b>Number of subjects in period 1</b> | Melanoma<br>400mg/q4w | TNBC 400mg/q4w | NSCLC 300mg/q3w |
|---------------------------------------|-----------------------|----------------|-----------------|
| Started                               | 61                    | 40             | 59              |
| Completed                             | 0                     | 0              | 0               |
| Not completed                         | 61                    | 40             | 59              |
| Adverse event, serious fatal          | 8                     | 4              | 10              |
| Physician decision                    | 9                     | 2              | 1               |
| Adverse event, non-fatal              | 3                     | 3              | 6               |
| Progressive Disease                   | 32                    | 31             | 39              |
| Subject/Guardian Decision             | 9                     | -              | 3               |

| <b>Number of subjects in period 1</b> | ATC 400 mg/q4w |
|---------------------------------------|----------------|
| Started                               | 42             |
| Completed                             | 0              |
| Not completed                         | 42             |
| Adverse event, serious fatal          | 9              |
| Physician decision                    | 3              |
| Adverse event, non-fatal              | 1              |
| Progressive Disease                   | 27             |
| Subject/Guardian Decision             | 2              |

## Baseline characteristics

| Reporting groups   |                    |
|--|--------------------|
| Reporting group title  | 1 mg/kg q2w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PDR001 1 mg/kg q2w                  |                    |
| Reporting group title  | 3 mg/kg q2w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q2w                  |                    |
| Reporting group title  | 10mg/kg q2w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w                 |                    |
| Reporting group title  | 3 mg/kg q4w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w                  |                    |
| Reporting group title  | 5 mg/kg q4w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 5 mg/kg q4w                  |                    |
| Reporting group title  | NSCLC 400mg/q4w    |
| Reporting group description:   |                    |
| Phase II: non-small cell cancer patients who took PDR001 400 mg/q4w                  |                    |
| Reporting group title  | Melanoma 400mg/q4w |
| Reporting group description:   |                    |
| Phase II: Melanoma patients who took PDR001 400 mg/q4w                               |                    |
| Reporting group title  | TNBC 400mg/q4w     |
| Reporting group description:   |                    |
| Phase II: Triple negative breast cancer (TNBC) patients who took PDR001 400 mg/q4w   |                    |
| Reporting group title  | NSCLC 300mg/q3w    |
| Reporting group description:   |                    |
| Phase II: non-small cell cancer patients who took PDR001 300 mg/q3w                  |                    |
| Reporting group title  | ATC 400 mg/q4w     |
| Reporting group description:   |                    |
| Patients in Phase II with anaplastic thyroid cancer (ATC) who took PDR001 400 mg/q4w |                    |

| Reporting group values     | 1 mg/kg q2w | 3 mg/kg q2w | 10mg/kg q2w |
|----------------------------|-------------|-------------|-------------|
| Number of subjects         | 16          | 15          | 11          |
| Age Categorical            |             |             |             |
| Units: Participants        |             |             |             |
| < 65 years                 | 12          | 9           | 8           |
| ≥ 65years                  | 4           | 6           | 3           |
| Sex: Female, Male          |             |             |             |
| Units: Participants        |             |             |             |
| Female                     | 9           | 7           | 4           |
| Male                       | 7           | 8           | 7           |
| Race/Ethnicity, Customized |             |             |             |
| Units: Subjects            |             |             |             |
| Caucasian                  | 10          | 14          | 8           |
| Black                      | 2           | 0           | 0           |
| Asian                      | 3           | 1           | 2           |



|         |   |   |   |
|---------|---|---|---|
| Unknown | 1 | 0 | 0 |
| Other   | 0 | 0 | 1 |

| Reporting group values                        | 3 mg/kg q4w | 5 mg/kg q4w | NSCLC 400mg/q4w |
|---|-------------|-------------|-----------------|
| Number of subjects                            | 6           | 10          | 59              |
| Age Categorical<br>Units: Participants        |             |             |                 |
| < 65 years                                    | 6           | 8           | 33              |
| ≥ 65years                                     | 0           | 2           | 26              |
| Sex: Female, Male<br>Units: Participants      |             |             |                 |
| Female  | 2           | 4           | 23              |
| Male  | 4           | 6           | 36              |
| Race/Ethnicity, Customized<br>Units: Subjects |             |             |                 |
| Caucasian                                     | 4           | 8           | 42              |
| Black   | 0           | 0           | 0               |
| Asian   | 2           | 1           | 12              |
| Unknown                                       | 0           | 0           | 5               |
| Other   | 0           | 1           | 0               |

| Reporting group values                        | Melanoma<br>400mg/q4w | TNBC 400mg/q4w | NSCLC 300mg/q3w |
|---|-----------------------|----------------|-----------------|
| Number of subjects                            | 61                    | 40             | 59              |
| Age Categorical<br>Units: Participants        |                       |                |                 |
| < 65 years                                    | 37                    | 29             | 35              |
| ≥ 65years                                     | 24                    | 11             | 24              |
| Sex: Female, Male<br>Units: Participants      |                       |                |                 |
| Female  | 22                    | 40             | 20              |
| Male  | 39                    | 0              | 39              |
| Race/Ethnicity, Customized<br>Units: Subjects |                       |                |                 |
| Caucasian                                     | 37                    | 32             | 50              |
| Black   | 1                     | 1              | 0               |
| Asian   | 23                    | 4              | 8               |
| Unknown                                       | 0                     | 2              | 1               |
| Other   | 0                     | 1              | 0               |

| Reporting group values                   | ATC 400 mg/q4w | Total |  |
|--|----------------|-------|--|
| Number of subjects                       | 42             | 319   |  |
| Age Categorical<br>Units: Participants   |                |       |  |
| < 65 years                               | 25             | 202   |  |
| ≥ 65years                                | 17             | 117   |  |
| Sex: Female, Male<br>Units: Participants |                |       |  |
| Female                                   | 19             | 150   |  |
| Male                                     | 23             | 169   |  |

|                            |    |     |  |
|----------------------------|----|-----|--|
| Race/Ethnicity, Customized |    |     |  |
| Units: Subjects            |    |     |  |
| Caucasian                  | 33 | 238 |  |
| Black                      | 1  | 5   |  |
| Asian                      | 4  | 60  |  |
| Unknown                    | 4  | 13  |  |
| Other                      | 0  | 3   |  |

### Subject analysis sets

|  |                     |
|--|---------------------|
| Subject analysis set title   | 10 mg/kg q2w        |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PDR001 10 mg/kg q2w       |                     |
| Subject analysis set title   | 3mg/kg q4w          |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w        |                     |
| Subject analysis set title   | 10 mg/kg q2w        |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w       |                     |
| Subject analysis set title   | 3mg/kg q4w          |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w        |                     |
| Subject analysis set title   | 10 mg/kg q2w        |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w       |                     |
| Subject analysis set title   | NSCLC 400 mg/q4w    |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w |                     |
| Subject analysis set title   | Melanoma 400 mg/q4w |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w              |                     |
| Subject analysis set title   | TNBC 400 mg/q4w     |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with TNBC who took PDR001 400 mg/q4w                  |                     |
| Subject analysis set title   | NSCLC 300 mg/q3w    |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w |                     |
| Subject analysis set title   | 10 mg/kg q2w        |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w       |                     |
| Subject analysis set title   | NSCLC 400 mg/q4w    |

|  |                             |
|--|-----------------------------|
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w   |                             |
| Subject analysis set title   | Melanoma 400 mg/q4w         |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w  |                             |
| Subject analysis set title   | TNBC 400 mg/q4w             |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with TNBC who took PDR001 400 mg/q4w  |                             |
| Subject analysis set title   | NSCLC 300 mg/q3w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w   |                             |
| Subject analysis set title   | 10 mg/kg q2w                |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w   |                             |
| Subject analysis set title   | 3mg/kg q4w                  |
| Subject analysis set type  | Full analysis               |
| Subject analysis set description:  |                             |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w  |                             |
| Subject analysis set title   | NSCLC 400 mg/q4w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w   |                             |
| Subject analysis set title   | Melanoma 400 mg/q4w         |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w  |                             |
| Subject analysis set title   | NSCLC 300 mg/q3w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w   |                             |
| Subject analysis set title   | NSCLC 400 mg/q4w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w   |                             |
| Subject analysis set title   | Melanoma 400 mg/q4w         |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w  |                             |
| Subject analysis set title   | NSCLC 300 mg/q3w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w   |                             |
| Subject analysis set title   | Phase 1 Part                |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| Combination of all the patients who were enrolled in the phase one part of the study. All the patients received varying doses of the study drug, PDR001. |                             |

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Phase 2 Part                |
| Subject analysis set type  | Modified intention-to-treat |

Subject analysis set description:

Combination of all the patients who were enrolled in the phase II part of the study. All the patients received varying doses of the study drug, PDR001.

| Reporting group values                        | 10 mg/kg q2w | 3mg/kg q4w | 10 mg/kg q2w |
|---|--------------|------------|--------------|
| Number of subjects                            | 11           | 6          | 4            |
| Age Categorical<br>Units: Participants        |              |            |              |
| < 65 years                                    | 8            | 6          |              |
| ≥ 65years                                     | 3            | 0          |              |
| Sex: Female, Male<br>Units: Participants      |              |            |              |
| Female  | 4            | 2          |              |
| Male  | 7            | 4          |              |
| Race/Ethnicity, Customized<br>Units: Subjects |              |            |              |
| Caucasian                                     | 8            | 4          |              |
| Black   | 0            | 0          |              |
| Asian   | 2            | 2          |              |
| Unknown                                       | 0            | 0          |              |
| Other   | 1            | 0          |              |

| Reporting group values                        | 3mg/kg q4w | 10 mg/kg q2w | NSCLC 400 mg/q4w |
|---|------------|--------------|------------------|
| Number of subjects                            | 3          | 11           | 59               |
| Age Categorical<br>Units: Participants        |            |              |                  |
| < 65 years                                    |            |              |                  |
| ≥ 65years                                     |            |              |                  |
| Sex: Female, Male<br>Units: Participants      |            |              |                  |
| Female  |            |              |                  |
| Male  |            |              |                  |
| Race/Ethnicity, Customized<br>Units: Subjects |            |              |                  |
| Caucasian                                     |            |              |                  |
| Black   |            |              |                  |
| Asian   |            |              |                  |
| Unknown                                       |            |              |                  |
| Other   |            |              |                  |

| Reporting group values                   | Melanoma 400 mg/q4w | TNBC 400 mg/q4w | NSCLC 300 mg/q3w |
|--|---------------------|-----------------|------------------|
| Number of subjects                       | 61                  | 40              | 59               |
| Age Categorical<br>Units: Participants   |                     |                 |                  |
| < 65 years                               |                     |                 |                  |
| ≥ 65years                                |                     |                 |                  |
| Sex: Female, Male<br>Units: Participants |                     |                 |                  |
| Female                                   |                     |                 |                  |

|      |  |  |  |
|------|--|--|--|
| Male |  |  |  |
|------|--|--|--|

|   |  |  |  |
|---|--|--|--|
| Race/Ethnicity, Customized<br>Units: Subjects |  |  |  |
| Caucasian                                     |  |  |  |
| Black   |  |  |  |
| Asian   |  |  |  |
| Unknown                                       |  |  |  |
| Other   |  |  |  |

| Reporting group values                        | 10 mg/kg q2w | NSCLC 400 mg/q4w | Melanoma 400 mg/q4w |
|---|--------------|------------------|---------------------|
| Number of subjects                            | 3            | 52               | 54                  |
| Age Categorical<br>Units: Participants        |              |                  |                     |
| < 65 years                                    |              |                  |                     |
| ≥ 65years                                     |              |                  |                     |
| Sex: Female, Male<br>Units: Participants      |              |                  |                     |
| Female  |              |                  |                     |
| Male  |              |                  |                     |
| Race/Ethnicity, Customized<br>Units: Subjects |              |                  |                     |
| Caucasian                                     |              |                  |                     |
| Black   |              |                  |                     |
| Asian   |              |                  |                     |
| Unknown                                       |              |                  |                     |
| Other   |              |                  |                     |

| Reporting group values                        | TNBC 400 mg/q4w | NSCLC 300 mg/q3w | 10 mg/kg q2w |
|---|-----------------|------------------|--------------|
| Number of subjects                            | 33              | 46               | 6            |
| Age Categorical<br>Units: Participants        |                 |                  |              |
| < 65 years                                    |                 |                  |              |
| ≥ 65years                                     |                 |                  |              |
| Sex: Female, Male<br>Units: Participants      |                 |                  |              |
| Female  |                 |                  |              |
| Male  |                 |                  |              |
| Race/Ethnicity, Customized<br>Units: Subjects |                 |                  |              |
| Caucasian                                     |                 |                  |              |
| Black   |                 |                  |              |
| Asian   |                 |                  |              |
| Unknown                                       |                 |                  |              |
| Other   |                 |                  |              |

| Reporting group values | 3mg/kg q4w | NSCLC 400 mg/q4w | Melanoma 400 mg/q4w |
|------------------------|------------|------------------|---------------------|
| Number of subjects     | 6          | 9                | 17                  |

|   |  |  |  |
|---|--|--|--|
| Age Categorical<br>Units: Participants          |  |  |  |
| < 65 years<br>≥ 65years                         |  |  |  |
| Sex: Female, Male<br>Units: Participants        |  |  |  |
| Female<br>Male                                  |  |  |  |
| Race/Ethnicity, Customized<br>Units: Subjects   |  |  |  |
| Caucasian<br>Black<br>Asian<br>Unknown<br>Other |  |  |  |

| <b>Reporting group values</b>                   | NSCLC 300 mg/q3w | NSCLC 400 mg/q4w | Melanoma 400 mg/q4w |
|---|------------------|------------------|---------------------|
| Number of subjects                              | 4                | 11               | 19                  |
| Age Categorical<br>Units: Participants          |                  |                  |                     |
| < 65 years<br>≥ 65years                         |                  |                  |                     |
| Sex: Female, Male<br>Units: Participants        |                  |                  |                     |
| Female<br>Male                                  |                  |                  |                     |
| Race/Ethnicity, Customized<br>Units: Subjects   |                  |                  |                     |
| Caucasian<br>Black<br>Asian<br>Unknown<br>Other |                  |                  |                     |

| <b>Reporting group values</b>                   | NSCLC 300 mg/q3w | Phase 1 Part | Phase 2 Part |
|---|------------------|--------------|--------------|
| Number of subjects                              | 5                | 58           | 261          |
| Age Categorical<br>Units: Participants          |                  |              |              |
| < 65 years<br>≥ 65years                         |                  |              |              |
| Sex: Female, Male<br>Units: Participants        |                  |              |              |
| Female<br>Male                                  |                  |              |              |
| Race/Ethnicity, Customized<br>Units: Subjects   |                  |              |              |
| Caucasian<br>Black<br>Asian<br>Unknown<br>Other |                  |              |              |



## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | 1 mg/kg q2w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PDR001 1 mg/kg q2w                  |                    |
| Reporting group title  | 3 mg/kg q2w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q2w                  |                    |
| Reporting group title  | 10mg/kg q2w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w                 |                    |
| Reporting group title  | 3 mg/kg q4w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w                  |                    |
| Reporting group title  | 5 mg/kg q4w        |
| Reporting group description:   |                    |
| Phase I Dose escalation cohort patients who took PRD001 5 mg/kg q4w                  |                    |
| Reporting group title  | NSCLC 400mg/q4w    |
| Reporting group description:   |                    |
| Phase II: non-small cell cancer patients who took PDR001 400 mg/q4w                  |                    |
| Reporting group title  | Melanoma 400mg/q4w |
| Reporting group description:   |                    |
| Phase II: Melanoma patients who took PDR001 400 mg/q4w                               |                    |
| Reporting group title  | TNBC 400mg/q4w     |
| Reporting group description:   |                    |
| Phase II: Triple negative breast cancer (TNBC) patients who took PDR001 400 mg/q4w   |                    |
| Reporting group title  | NSCLC 300mg/q3w    |
| Reporting group description:   |                    |
| Phase II: non-small cell cancer patients who took PDR001 300 mg/q3w                  |                    |
| Reporting group title  | ATC 400 mg/q4w     |
| Reporting group description:   |                    |
| Patients in Phase II with anaplastic thyroid cancer (ATC) who took PDR001 400 mg/q4w |                    |
| Subject analysis set title   | 10 mg/kg q2w       |
| Subject analysis set type  | Full analysis      |
| Subject analysis set description:  |                    |
| Phase I Dose escalation cohort patients who took PDR001 10 mg/kg q2w                 |                    |
| Subject analysis set title   | 3mg/kg q4w         |
| Subject analysis set type  | Full analysis      |
| Subject analysis set description:  |                    |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w                  |                    |
| Subject analysis set title   | 10 mg/kg q2w       |
| Subject analysis set type  | Sub-group analysis |
| Subject analysis set description:  |                    |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w                 |                    |
| Subject analysis set title   | 3mg/kg q4w         |
| Subject analysis set type  | Sub-group analysis |
| Subject analysis set description:  |                    |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w                  |                    |
| Subject analysis set title   | 10 mg/kg q2w       |



|  |                     |
|--|---------------------|
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w       |                     |
| Subject analysis set title   | NSCLC 400 mg/q4w    |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w |                     |
| Subject analysis set title   | Melanoma 400 mg/q4w |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w              |                     |
| Subject analysis set title   | TNBC 400 mg/q4w     |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with TNBC who took PDR001 400 mg/q4w                  |                     |
| Subject analysis set title   | NSCLC 300 mg/q3w    |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w |                     |
| Subject analysis set title   | 10 mg/kg q2w        |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w       |                     |
| Subject analysis set title   | NSCLC 400 mg/q4w    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w |                     |
| Subject analysis set title   | Melanoma 400 mg/q4w |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w              |                     |
| Subject analysis set title   | TNBC 400 mg/q4w     |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients in Phase II with TNBC who took PDR001 400 mg/q4w                  |                     |
| Subject analysis set title   | NSCLC 300 mg/q3w    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w |                     |
| Subject analysis set title   | 10 mg/kg q2w        |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w       |                     |
| Subject analysis set title   | 3mg/kg q4w          |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w        |                     |
| Subject analysis set title   | NSCLC 400 mg/q4w    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w |                     |
| Subject analysis set title   | Melanoma 400 mg/q4w |

|  |                             |
|--|-----------------------------|
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w  |                             |
| Subject analysis set title   | NSCLC 300 mg/q3w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w   |                             |
| Subject analysis set title   | NSCLC 400 mg/q4w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 400 mg/q4w   |                             |
| Subject analysis set title   | Melanoma 400 mg/q4w         |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with Melanoma who took PDR001 400 mg/q4w  |                             |
| Subject analysis set title   | NSCLC 300 mg/q3w            |
| Subject analysis set type  | Sub-group analysis          |
| Subject analysis set description:  |                             |
| Patients in Phase II with non-small cell cancer who took PDR001 300 mg/q3w   |                             |
| Subject analysis set title   | Phase 1 Part                |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| Combination of all the patients who were enrolled in the phase one part of the study. All the patients received varying doses of the study drug, PDR001. |                             |
| Subject analysis set title   | Phase 2 Part                |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| Combination of all the patients who were enrolled in the phase II part of the study. All the patients received varying doses of the study drug, PDR001.  |                             |

**Primary: Phase I: The exposure (AUC(0-336h)) after first dose of treatment at cycle 3 (each cycle = 28 days)**

|  |   |
|--|---|
| End point title  | Phase I: The exposure (AUC(0-336h)) after first dose of treatment at cycle 3 (each cycle = 28 days) <sup>[1][2]</sup> |
| End point description:   |   |
| Estimated the recommended phase 2 dose (RP2D) and/or the maximum tolerated dose (MTD) for PDR001.      |   |
| AUC0-336h is the AUC from time zero to 336 hour post dose of a measurable concentration sampling time. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (cycle 3)                                |   |

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: No statistical analysis planned

[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: No statistical analysis planned

| End point values                                    | 1 mg/kg q2w     | 3 mg/kg q2w     | 5 mg/kg q4w     | 10 mg/kg q2w         |
|---|-----------------|-----------------|-----------------|----------------------|
| Subject group type                                  | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed                         | 8               | 4               | 4               | 4                    |
| Units: day*ug/mL                                    |                 |                 |                 |                      |
| geometric mean (geometric coefficient of variation) | 270 (± 52.5)    | 1150 (± 51.1)   | 1490 (± 34.2)   | 3110 (± 33.1)        |

| End point values                                    | 3mg/kg q4w           |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 3                    |  |  |  |
| Units: day*ug/mL                                    |                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 575 (± 21.8)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Phase I: Incidence of dose limiting toxicities (DLTs)

|                 |   |
|-----------------|---|
| End point title | Phase I: Incidence of dose limiting toxicities (DLTs) <sup>[3][4]</sup> |
|-----------------|---|

End point description:

DLT is defined as an adverse event (AE) or abnormal laboratory value of common terminology criteria for adverse events (CTCAE) grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness or concomitant medications, which occurs within the first cycle of treatment with PDR001 during the dose escalation part of the study for which relationship to study treatment cannot be ruled out, with some exceptions.

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

End point timeframe:

8 months

Notes:

[3] - 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: No statistical analysis planned

[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: No statistical analysis planned

| End point values            | 1 mg/kg q2w     | 3 mg/kg q2w     | 5 mg/kg q4w     | 10 mg/kg q2w         |
|-----------------------------|-----------------|-----------------|-----------------|----------------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 16              | 15              | 10              | 11                   |
| Units: Participants         | 0               | 0               | 0               | 0                    |

| End point values            | 3mg/kg q4w           |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 6                    |  |  |  |

|                     |   |  |  |  |
|---------------------|---|--|--|--|
| Units: Participants | 0 |  |  |  |
|---------------------|---|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Phase II: Overall response Rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

|                 |  |
|-----------------|--|
| End point title | Phase II: Overall response Rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) <sup>[5][6]</sup> |
|-----------------|--|

End point description:

ORR is the percentage of participants with a best overall response of complete response (CR) or partial response (PR) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

CR = at least 2 determinations of CR at least 4 weeks apart before progression where confirmation required or 1 determination of CR prior to progression where confirmation not required.

PR = at least 2 determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or 1 determination of PR prior to progression where confirmation not required.

RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

61 months

Notes:

[5] - 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: No statistical analysis planned

[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: No statistical analysis planned

| End point values                  | ATC 400 mg/q4w     | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-----------------------------------|--------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group    | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed       | 42                 | 59                   | 61                   | 40                   |
| Units: Percentage of participants |                    |                      |                      |                      |
| number (confidence interval 90%)  | 19.0 (9.8 to 31.8) | 15.3 (8.2 to 25.1)   | 27.9 (18.6 to 38.8)  | 0.0 (0.0 to 7.2)     |

| End point values                  | NSCLC 300 mg/q3w     |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 59                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| number (confidence interval 90%)  | 6.8 (2.3 to 14.8)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I: Serum pharmacokinetic (PK) parameter AUCs (AUC0-336h (cycle 1 only), AUCinf, AUClast AUCtau)

|                 |  |
|-----------------|--|
| End point title | Phase I: Serum pharmacokinetic (PK) parameter AUCs (AUC0-336h (cycle 1 only), AUCinf, AUClast AUCtau) <sup>[7]</sup> |
|-----------------|--|

End point description:

AUC0-336h is the AUC from time zero to 336 hour post dose of a measurable concentration sampling time.

AUClast: The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1).

AUCinf: The AUC from time zero to infinity (mass x time x volume-1).

AUCtau: The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1).

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

End point timeframe:

Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (cycle 1 & 3)

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: No statistical analysis planned

| End point values                                    | 1 mg/kg q2w     | 3 mg/kg q2w     | 5 mg/kg q4w     | 10 mg/kg q2w         |
|---|-----------------|-----------------|-----------------|----------------------|
| Subject group type                                  | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed                         | 16              | 15              | 10              | 11                   |
| Units: day*ug/mL                                    |                 |                 |                 |                      |
| geometric mean (geometric coefficient of variation) |                 |                 |                 |                      |
| Cycle (C) 1: AUC0-336h (n=16, 13, 10, 6, 10)        | 126 (± 29.5)    | 324 (± 24.4)    | 638 (± 35.3)    | 1270 (± 20.3)        |
| C1: AUCinf (n = 1, 0,0,2,3)                         | 123 (± 0)       | 999 (± 999)     | 726 (± 16.0)    | 999 (± 999)          |
| C1: AUClast   | 125 (± 29.9)    | 353 (± 31.4)    | 943 (± 37.4)    | 1240 (± 21.6)        |
| C1: AUCtau (n = 16, 13, 10, 6, 10)                  | 126 (± 29.5)    | 324 (± 24.4)    | 984 (± 41.9)    | 1270 (± 20.3)        |
| C3: AUClast   | 260 (± 44.8)    | 995 (± 60.5)    | 2560 (± 37.2)   | 2520 (± 58.4)        |
| C3: AUCtau (n = 8, 4, 4, 2, 2)                      | 270 (± 52.5)    | 1150 (± 51.1)   | 2770 (± 26.6)   | 3110 (± 33.1)        |

| End point values                                    | 3mg/kg q4w           |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 6                    |  |  |  |
| Units: day*ug/mL                                    |                      |  |  |  |
| geometric mean (geometric coefficient of variation) |                      |  |  |  |
| Cycle (C) 1: AUC0-336h (n=16, 13, 10, 6, 10)        | 350 (± 35.0)         |  |  |  |
| C1: AUCinf (n = 1, 0,0,2,3)                         | 384 (± 9.8)          |  |  |  |
| C1: AUClast   | 522 (± 39.1)         |  |  |  |
| C1: AUCtau (n = 16, 13, 10, 6, 10)                  | 524 (± 39.6)         |  |  |  |
| C3: AUClast   | 933 (± 21.3)         |  |  |  |
| C3: AUCtau (n = 8, 4, 4, 2, 2)                      | 1040 (± 19.1)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I: Serum pharmacokinetic (PK) parameter Cmax

End point title Phase I: Serum pharmacokinetic (PK) parameter Cmax<sup>[8]</sup>

End point description:

The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume<sup>-1</sup>)

End point type Secondary

End point timeframe:

Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (Cycle 1 & 3)

Notes:

[8] - 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: No statistical analysis planned

| End point values                                    | 1 mg/kg q2w     | 3 mg/kg q2w     | 5 mg/kg q4w     | 10 mg/kg q2w         |
|---|-----------------|-----------------|-----------------|----------------------|
| Subject group type                                  | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed                         | 16              | 15              | 10              | 11                   |
| Units: ug/mL  |                 |                 |                 |                      |
| geometric mean (geometric coefficient of variation) |                 |                 |                 |                      |
| C1 (n = 15, 15, 10, 6, 9)                           | 18.2 (± 26.5)   | 53.8 (± 23.6)   | 106 (± 34.2)    | 185 (± 18.3)         |
| C3 (n = 10, 7, 3, 3, 2)                             | 29.7 (± 41.0)   | 112 (± 27.3)    | 179 (± 45.2)    | 312 (± 30.0)         |

| End point values                                    | 3mg/kg q4w           |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 6                    |  |  |  |
| Units: ug/mL  |                      |  |  |  |
| geometric mean (geometric coefficient of variation) |                      |  |  |  |
| C1 (n = 15, 15, 10, 6, 9)                           | 53.8 (± 29.4)        |  |  |  |
| C3 (n = 10, 7, 3, 3, 2)                             | 69.7 (± 9.4)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I: Serum pharmacokinetic (PK) parameter Tmax

End point title Phase I: Serum pharmacokinetic (PK) parameter Tmax<sup>[9]</sup>

End point description:

The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

End point type Secondary

End point timeframe:

Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (cycle 1 & 3)

Notes:

[9] - 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: No statistical analysis planned

| End point values              | 1 mg/kg q2w         | 3 mg/kg q2w         | 5 mg/kg q4w         | 10 mg/kg q2w         |
|-------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type            | Reporting group     | Reporting group     | Reporting group     | Subject analysis set |
| Number of subjects analysed   | 16                  | 15                  | 10                  | 11                   |
| Units: hour                   |                     |                     |                     |                      |
| median (full range (min-max)) |                     |                     |                     |                      |
| C1 (n = 15, 15, 10, 6, 9)     | 1.58 (1.38 to 2.12) | 1.57 (1.25 to 1.7)  | 1.58 (1.08 to 1.67) | 1.55 (1.13 to 1.68)  |
| C3 (n = 10, 7, 3, 3, 2)       | 1.55 (1.45 to 1.75) | 1.55 (0.75 to 1.58) | 1.3 (0.783 to 1.82) | 1.58 (1.52 to 1.62)  |

| End point values              | 3mg/kg q4w           |  |  |  |
|-------------------------------|----------------------|--|--|--|
| Subject group type            | Subject analysis set |  |  |  |
| Number of subjects analysed   | 6                    |  |  |  |
| Units: hour                   |                      |  |  |  |
| median (full range (min-max)) |                      |  |  |  |
| C1 (n = 15, 15, 10, 6, 9)     | 1.55 (1.5 to 1.83)   |  |  |  |
| C3 (n = 10, 7, 3, 3, 2)       | 1.5 (1.5 to 1.57)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Serum pharmacokinetic (PK) parameter AUCs (AUC336h, AUCinf, AUClast, AUCtau)

End point title Phase II: Serum pharmacokinetic (PK) parameter AUCs (AUC336h, AUCinf, AUClast, AUCtau)<sup>[10]</sup>

End point description:

AUC0-336h is the AUC from time zero to 336 hour post dose of a measurable concentration sampling time.

AUClast: The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1).

AUCinf: The AUC from time zero to infinity (mass x time x volume-1).

AUCtau: The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1).

End point type Secondary

End point timeframe:

Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (cycle 1 & 3)

Notes:

[10] - 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: No statistical analysis planned

| End point values                                    | ATC 400<br>mg/q4w | NSCLC 400<br>mg/q4w  | Melanoma 400<br>mg/q4w | TNBC 400<br>mg/q4w   |
|---|-------------------|----------------------|------------------------|----------------------|
| Subject group type                                  | Reporting group   | Subject analysis set | Subject analysis set   | Subject analysis set |
| Number of subjects analysed                         | 42                | 59                   | 61                     | 40                   |
| Units: day*ug/mL                                    |                   |                      |                        |                      |
| geometric mean (geometric coefficient of variation) |                   |                      |                        |                      |
| C1: AUC0-336h (n = 58, 58, 37, 54, 37)              | 704 (± 28.2)      | 681 (± 39.4)         | 775 (± 31.7)           | 752 (± 29.3)         |
| C1: AUCinf (n = 13, 8, 7, 5, 2)                     | 1160 (± 7.1)      | 1090 (± 29.6)        | 1080 (± 45.4)          | 1240 (± 25.2)        |
| C1: AUClast   | 865 (± 69.8)      | 980 (± 42.5)         | 1020 (± 109.9)         | 923 (± 76.1)         |
| C1: AUCtau (n= 54, 55, 32, 48, 36)                  | 1070 (± 31.3)     | 1010 (± 39.8)        | 1190 (± 35.0)          | 1130 (± 34.9)        |
| C3: AUC0-336h (n = 36, 49, 12, 40, 16)              | 1290 (± 30.0)     | 1210 (± 36.3)        | 1140 (± 43.8)          | 1360 (± 45.7)        |
| C3: AUCinf (n = 1, 1, 1, 1, 0)                      | 999 (± 999)       | 1050 (± 999)         | 1070 (± 999)           | 2340 (± 999)         |
| C3: AUClast (n = 37, 51, 16, 44, 19)                | 1600 (± 88.0)     | 1860 (± 39.9)        | 1650 (± 59.7)          | 1630 (± 73.4)        |
| C3: AUCtau (n= 31, 44, 7, 38, 14)                   | 2120 (± 32.7)     | 1940 (± 35.5)        | 1790 (± 53.4)          | 1920 (± 44.4)        |

| End point values                                    | NSCLC 300<br>mg/q3w  |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 59                   |  |  |  |
| Units: day*ug/mL                                    |                      |  |  |  |
| geometric mean (geometric coefficient of variation) |                      |  |  |  |
| C1: AUC0-336h (n = 58, 58, 37, 54, 37)              | 535 (± 29.3)         |  |  |  |
| C1: AUCinf (n = 13, 8, 7, 5, 2)                     | 491 (± 22.7)         |  |  |  |
| C1: AUClast   | 602 (± 62.2)         |  |  |  |
| C1: AUCtau (n= 54, 55, 32, 48, 36)                  | 689 (± 40.4)         |  |  |  |
| C3: AUC0-336h (n = 36, 49, 12, 40, 16)              | 850 (± 50.6)         |  |  |  |
| C3: AUCinf (n = 1, 1, 1, 1, 0)                      | 135 (± 999)          |  |  |  |
| C3: AUClast (n = 37, 51, 16, 44, 19)                | 984 (± 78.0)         |  |  |  |
| C3: AUCtau (n= 31, 44, 7, 38, 14)                   | 1100 (± 54.5)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Serum pharmacokinetic (PK) parameter Cmax

|   |   |
|---|---|
| End point title   | Phase II: Serum pharmacokinetic (PK) parameter Cmax <sup>[11]</sup> |
| End point description:  |   |
| The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1) |   |
| End point type  | Secondary   |



End point timeframe:

Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (Cycle 1 & 3)

Notes:

[11] - 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: No statistical analysis planned

| End point values                                    | ATC 400 mg/q4w  | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|---|-----------------|----------------------|----------------------|----------------------|
| Subject group type                                  | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed                         | 42              | 59                   | 61                   | 40                   |
| Units: ug/mL  |                 |                      |                      |                      |
| geometric mean (geometric coefficient of variation) |                 |                      |                      |                      |
| C1 (n = 52, 58, 32, 55, 35)                         | 100 (± 27.3)    | 103 (± 37.0)         | 111 (± 26.6)         | 114 (± 23.6)         |
| C3 (n = 33, 45, 11, 39, 18)                         | 146 (± 22.6)    | 151 (± 32.0)         | 141 (± 33.4)         | 163 (± 34.7)         |

| End point values                                    | NSCLC 300 mg/q3w     |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 59                   |  |  |  |
| Units: ug/mL  |                      |  |  |  |
| geometric mean (geometric coefficient of variation) |                      |  |  |  |
| C1 (n = 52, 58, 32, 55, 35)                         | 79.9 (± 31.8)        |  |  |  |
| C3 (n = 33, 45, 11, 39, 18)                         | 103 (± 36.6)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Serum pharmacokinetic (PK) parameter Tmax

|                 |   |
|-----------------|---|
| End point title | Phase II: Serum pharmacokinetic (PK) parameter Tmax <sup>[12]</sup> |
|-----------------|---|

End point description:

The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

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

End point timeframe:

Predose, 1hour (h), 24h, 48h, 72h, 168h, 240h, 336h post dose (Cycle 1 & 3)

Notes:

[12] - 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: No statistical analysis planned

| End point values              | ATC 400 mg/q4w     | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-------------------------------|--------------------|----------------------|----------------------|----------------------|
| Subject group type            | Reporting group    | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed   | 42                 | 59                   | 61                   | 40                   |
| Units: hour                   |                    |                      |                      |                      |
| median (full range (min-max)) |                    |                      |                      |                      |
| C1 (n= 52, 58, 32, 55, 35)    | 1.55 (0.5 to 2.75) | 1.58 (0.55 to 2.52)  | 1.58 (1.07 to 2.9)   | 1.58 (1.18 to 2.15)  |
| C3 (n = 33, 45, 11, 39, 18)   | 1.57 (0 to 4.63)   | 1.6 (0.983 to 2.08)  | 1.55 (1.07 to 2.22)  | 1.53 (1.42 to 1.62)  |

| End point values              | NSCLC 300 mg/q3w     |  |  |  |
|-------------------------------|----------------------|--|--|--|
| Subject group type            | Subject analysis set |  |  |  |
| Number of subjects analysed   | 59                   |  |  |  |
| Units: hour                   |                      |  |  |  |
| median (full range (min-max)) |                      |  |  |  |
| C1 (n= 52, 58, 32, 55, 35)    | 1.65 (1.00 to 3.08)  |  |  |  |
| C3 (n = 33, 45, 11, 39, 18)   | 1.58 (1.33 to 2.92)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I: Presence and/or concentration of anti-PDR001

|                 |   |
|-----------------|---|
| End point title | Phase I: Presence and/or concentration of anti-PDR001 <sup>[13]</sup> |
|-----------------|---|

End point description:

Assessed PDR001 anti-drug anti-body (ADA) incidence in Phase I patients - the emergence of anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of PDR001. Each cycle = 28 days; End of treatment was expected to be on average 1 year after the start of study treatment. For Treatment-induced ADA-positive, percentage was based on patients ADA-negative at baseline. For Treatment-boosted ADA-positive, percentage was based on patients ADA-positive at baseline.

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

End point timeframe:

42 months

Notes:

[13] - 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: No statistical analysis planned

| End point values                              | 1 mg/kg q2w     | 3 mg/kg q2w     | 5 mg/kg q4w     | 10 mg/kg q2w         |
|---|-----------------|-----------------|-----------------|----------------------|
| Subject group type                            | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed                   | 16              | 11              | 10              | 3                    |
| Units: Participants                           |                 |                 |                 |                      |
| Patients with ADA-negative sample at baseline | 11              | 9               | 9               | 1                    |
| Patients with ADA-positive sample at baseline | 5               | 2               | 1               | 2                    |

|                                    |    |   |   |   |
|------------------------------------|----|---|---|---|
| ADA-negative                       | 10 | 8 | 8 | 1 |
| ADA-positive (i.e., ADA incidence) | 4  | 2 | 1 | 2 |
| Treatment-induced ADA-positive     | 1  | 1 | 1 | 0 |
| Treatment-boosted ADA-positive     | 3  | 1 | 0 | 2 |

| End point values                              | 3mg/kg q4w           |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                            | Subject analysis set |  |  |  |
| Number of subjects analysed                   | 6                    |  |  |  |
| Units: Participants                           |                      |  |  |  |
| Patients with ADA-negative sample at baseline | 5                    |  |  |  |
| Patients with ADA-positive sample at baseline | 1                    |  |  |  |
| ADA-negative                                  | 4                    |  |  |  |
| ADA-positive (i.e., ADA incidence)            | 1                    |  |  |  |
| Treatment-induced ADA-positive                | 1                    |  |  |  |
| Treatment-boosted ADA-positive                | 0                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Presence and/or concentration of anti-PDR001

|                 |  |
|-----------------|--|
| End point title | Phase II: Presence and/or concentration of anti-PDR001 <sup>[14]</sup> |
|-----------------|--|

End point description:

Assessed PDR001 anti-drug anti-body (ADA) incidence in Phase I patients - the emergence of anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of PDR001. Each cycle = 28 days; End of treatment was expected to be on average 1 year after the start of study treatment. For Treatment -induced ADA-positive, Percentage was based on subjects ADA-negative at baseline. For Treatment-boosted ADA-positive, Percentage was based on subjects ADA-positive at baseline.

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

End point timeframe:

42 months

Notes:

[14] - 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: No statistical analysis planned

| End point values                              | ATC 400 mg/q4w  | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|---|-----------------|----------------------|----------------------|----------------------|
| Subject group type                            | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed                   | 31              | 52                   | 54                   | 33                   |
| Units: Participants                           |                 |                      |                      |                      |
| Patients with ADA-negative sample at baseline | 29              | 43                   | 48                   | 29                   |
| Patients with ADA-positive sample at baseline | 2               | 9                    | 6                    | 4                    |
| ADA-negative                                  | 24              | 34                   | 46                   | 23                   |
| ADA-positive (i.e., ADA incidence)            | 6               | 11                   | 4                    | 7                    |

|                                |   |   |   |   |
|--------------------------------|---|---|---|---|
| Treatment-induced ADA-positive | 5 | 9 | 2 | 6 |
| Treatment-boosted ADA-positive | 1 | 2 | 2 | 1 |

| End point values                              | NSCLC 300 mg/q3w     |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                            | Subject analysis set |  |  |  |
| Number of subjects analysed                   | 46                   |  |  |  |
| Units: Participants                           |                      |  |  |  |
| Patients with ADA-negative sample at baseline | 41                   |  |  |  |
| Patients with ADA-positive sample at baseline | 5                    |  |  |  |
| ADA-negative                                  | 31                   |  |  |  |
| ADA-positive (i.e., ADA incidence)            | 12                   |  |  |  |
| Treatment-induced ADA-positive                | 10                   |  |  |  |
| Treatment-boosted ADA-positive                | 2                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I: Overall Response Rate (ORR) as per Investigator based on RECIST v1.1

|                 |   |
|-----------------|---|
| End point title | Phase I: Overall Response Rate (ORR) as per Investigator based on RECIST v1.1 <sup>[15]</sup> |
|-----------------|---|

End point description:

ORR is the percentage of participants with a best overall response of complete response CR or partial response PR as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required.

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

27 months

Notes:

[15] - 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: No statistical analysis planned

| End point values                  | 1 mg/kg q2w        | 3 mg/kg q2w       | 5 mg/kg q4w       | 10 mg/kg q2w         |
|-----------------------------------|--------------------|-------------------|-------------------|----------------------|
| Subject group type                | Reporting group    | Reporting group   | Reporting group   | Subject analysis set |
| Number of subjects analysed       | 16                 | 15                | 10                | 11                   |
| Units: Percentage of participants |                    |                   |                   |                      |
| number (confidence interval 90%)  | 0.00 (0.0 to 17.1) | 6.7 (0.3 to 27.9) | 0.0 (0.0 to 25.9) | 9.1 (0.5 to 36.4)    |

|                                   |                      |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| <b>End point values</b>           | 3mg/kg q4w           |  |  |  |
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 6                    |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| number (confidence interval 90%)  | 0.0 (0.0 to 39.3)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I: Disease Control Rate (DCR) as per Investigator based on RECIST v1.1

|                 |  |
|-----------------|--|
| End point title | Phase I: Disease Control Rate (DCR) as per Investigator based on RECIST v1.1 <sup>[16]</sup> |
|-----------------|--|

End point description:

DCR is the percentage of patients with a best overall response of CR or PR or stable disease (SD).

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

27 months

Notes:

[16] - 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: No statistical analysis planned

|                                   |                     |                     |                     |                    |
|-----------------------------------|---------------------|---------------------|---------------------|--------------------|
| <b>End point values</b>           | 1 mg/kg q2w         | 3 mg/kg q2w         | 3 mg/kg q4w         | 5 mg/kg q4w        |
| Subject group type                | Reporting group     | Reporting group     | Reporting group     | Reporting group    |
| Number of subjects analysed       | 16                  | 15                  | 6                   | 10                 |
| Units: Percentage of participants |                     |                     |                     |                    |
| number (confidence interval 90%)  | 56.3 (33.3 to 77.3) | 46.7 (24.4 to 70.0) | 50.0 (15.3 to 84.7) | 20.0 (3.7 to 50.7) |

|                                   |                      |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| <b>End point values</b>           | 10 mg/kg q2w         |  |  |  |
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 11                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| number (confidence interval 90%) | 27.3 (7.9 to 56.4) |  |  |  |
|----------------------------------|--------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I: Progression Free Survival (PFS) as per RECIST v1.1

|                 |   |
|-----------------|---|
| End point title | Phase I: Progression Free Survival (PFS) as per RECIST v1.1 <sup>[17]</sup> |
|-----------------|---|

End point description:

PFS is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. PFS is per Kaplan-Meier estimates.

RECIST criteria, published in February 2000 by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group, is a Response evaluation criteria in solid tumors is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

27 months

Notes:

[17] - 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: No statistical analysis planned

| End point values                  | 1 mg/kg q2w      | 3 mg/kg q2w      | 5 mg/kg q4w      | 10 mg/kg q2w         |
|-----------------------------------|------------------|------------------|------------------|----------------------|
| Subject group type                | Reporting group  | Reporting group  | Reporting group  | Subject analysis set |
| Number of subjects analysed       | 16               | 15               | 10               | 6                    |
| Units: Percentage of participants |                  |                  |                  |                      |
| median (confidence interval 90%)  | 3.5 (1.8 to 6.5) | 1.9 (1.5 to 8.1) | 1.8 (1.1 to 1.8) | 2.2 (1.7 to 5.8)     |

| End point values                  | 3mg/kg q4w           |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 11                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| median (confidence interval 90%)  | 2.7 (1.1 to 3.5)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I: Duration of Response (DOR) as per RECIST v1.1

|                 |  |
|-----------------|--|
| End point title | Phase I: Duration of Response (DOR) as per RECIST v1.1 <sup>[18]</sup> |
|-----------------|--|

End point description:

DOR: measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented. CR = at least 2 determinations of CR at least 4 weeks apart before progression where confirmation required or 1 determination of CR prior to progression where confirmation not required; PR = at least 2 determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or 1 determination of PR prior to progression where confirmation not required; PD = progression ≤ 12 weeks after randomization/start of treatment (and not qualifying for CR, PR or SD). SD = at least 1 SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR). RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment

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

End point timeframe:

61 months

Notes:

[18] - 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: No statistical analysis planned

|  |                         |                      |  |  |
|--|-------------------------|----------------------|--|--|
| <b>End point values</b>                | 3 mg/kg q2w             | 10mg/kg q2w          |  |  |
| Subject group type                     | Reporting group         | Reporting group      |  |  |
| Number of subjects analysed            | 1                       | 1                    |  |  |
| Units: months                          |                         |                      |  |  |
| arithmetic mean (full range (min-max)) | 261.00 (261.0 to 261.0) | 55.00 (55.0 to 55.0) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I only: Overall Response Rate (ORR) as per Investigator based on immune related response criteria (irRC)

|                 |  |
|-----------------|--|
| End point title | Phase I only: Overall Response Rate (ORR) as per Investigator based on immune related response criteria (irRC) <sup>[19]</sup> |
|-----------------|--|

End point description:

ORR is the percentage of participants with a best overall response of complete response (CR) or partial response (PR) as per irRC.

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required.

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

The immune-related response criteria (irRC) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug.

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

End point timeframe:

27 months

Notes:

[19] - 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: No statistical analysis planned

| End point values                  | 1 mg/kg q2w        | 3 mg/kg q2w       | 10mg/kg q2w       | 5 mg/kg q4w       |
|-----------------------------------|--------------------|-------------------|-------------------|-------------------|
| Subject group type                | Reporting group    | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed       | 16                 | 15                | 11                | 10                |
| Units: Percentage of participants |                    |                   |                   |                   |
| number (confidence interval 90%)  | 0.00 (0.0 to 17.1) | 6.7 (0.3 to 27.9) | 9.1 (0.5 to 36.4) | 0.0 (0.0 to 25.9) |

| End point values                  | 3mg/kg q4w           |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 6                    |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| number (confidence interval 90%)  | 0.0 (0.0 to 39.3)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase I only: Disease Control Rate (DCR) as per Investigator based on irRC

|                 |  |
|-----------------|--|
| End point title | Phase I only: Disease Control Rate (DCR) as per Investigator based on irRC <sup>[20]</sup> |
|-----------------|--|

End point description:

DCR is the percentage of patients with a best overall response of CR or PR or stable disease (SD).  
CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required  
PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.  
SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).  
The immune-related response criteria (irRC) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug.

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

End point timeframe:

27 months

Notes:

[20] - 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: No statistical analysis planned

| End point values                  | 1 mg/kg q2w         | 3 mg/kg q2w         | 10mg/kg q2w        | 3 mg/kg q4w         |
|-----------------------------------|---------------------|---------------------|--------------------|---------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group    | Reporting group     |
| Number of subjects analysed       | 16                  | 15                  | 11                 | 6                   |
| Units: Percentage of participants |                     |                     |                    |                     |
| number (confidence interval 90%)  | 62.5 (39.1 to 82.2) | 53.3 (30.0 to 75.6) | 27.3 (7.9 to 56.4) | 50.0 (15.3 to 84.7) |



|                                   |                    |  |  |  |
|-----------------------------------|--------------------|--|--|--|
| <b>End point values</b>           | 5 mg/kg q4w        |  |  |  |
| Subject group type                | Reporting group    |  |  |  |
| Number of subjects analysed       | 10                 |  |  |  |
| Units: Percentage of participants |                    |  |  |  |
| number (confidence interval 90%)  | 30.0 (8.7 to 60.7) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I only: Progression Free Survival (PFS) as per irRC

|                 |   |
|-----------------|---|
| End point title | Phase I only: Progression Free Survival (PFS) as per irRC <sup>[21]</sup> |
|-----------------|---|

End point description:

PFS is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. PFS is per Kaplan-Meier estimates.

The immune-related response criteria (irRC) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug.

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

End point timeframe:

27 months

Notes:

[21] - 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: No statistical analysis planned

|                                   |                  |                  |                  |                      |
|-----------------------------------|------------------|------------------|------------------|----------------------|
| <b>End point values</b>           | 1 mg/kg q2w      | 3 mg/kg q2w      | 5 mg/kg q4w      | 10 mg/kg q2w         |
| Subject group type                | Reporting group  | Reporting group  | Reporting group  | Subject analysis set |
| Number of subjects analysed       | 16               | 15               | 10               | 11                   |
| Units: Percentage of participants |                  |                  |                  |                      |
| median (confidence interval 90%)  | 3.6 (1.8 to 999) | 2.7 (1.5 to 8.1) | 1.8 (1.1 to 2.8) | 2.2 (1.7 to 5.8)     |

|                                   |                      |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| <b>End point values</b>           | 3mg/kg q4w           |  |  |  |
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 11                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| median (confidence interval 90%)  | 2.7 (1.1 to 5.2)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I: Duration of Response (DOR) as per irRC

|                 |   |
|-----------------|---|
| End point title | Phase I: Duration of Response (DOR) as per irRC <sup>[22]</sup> |
|-----------------|---|

End point description:

DOR: measured from time measurement criteria are met for CR or PR (whichever status is recorded first) until first date that recurrence or PD is objectively documented

CR: at least 2 determinations of CR at least 4 weeks apart before progression where confirmation required or 1 determination of CR prior to progression where confirmation not required

PR: at least 1 determination of PR or better at least 4 weeks apart before progression (& not qualifying for a CR) where confirmation required or 1 determination of PR prior to progression where confirmation not required

PD: progression ≤ start of treatment (& not qualifying for CR, PR or SD)

SD: at least 1 SD assessment (or better) > 6 weeks after randomization/start of treatment (& not qualifying for CR or PR)

irRC is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug

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

End point timeframe:

61 months

Notes:

[22] - 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: No statistical analysis planned

| End point values                       | 3 mg/kg q2w             | 10mg/kg q2w          |  |  |
|--|-------------------------|----------------------|--|--|
| Subject group type                     | Reporting group         | Reporting group      |  |  |
| Number of subjects analysed            | 1                       | 1                    |  |  |
| Units: months                          |                         |                      |  |  |
| arithmetic mean (full range (min-max)) | 261.00 (261.0 to 261.0) | 55.00 (55.0 to 55.0) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase II: Disease control rate (DCR) as per Investigator based on RECIST v1.1

|                 |   |
|-----------------|---|
| End point title | Phase II: Disease control rate (DCR) as per Investigator based on RECIST v1.1 <sup>[23]</sup> |
|-----------------|---|

End point description:

DCR is the percentage of patients with a best overall response of CR or PR or stable disease (SD).

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

61 months

Notes:

[23] - 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: No statistical analysis planned

| End point values                  | ATC 400 mg/q4w      | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-----------------------------------|---------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group     | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed       | 42                  | 59                   | 61                   | 40                   |
| Units: Percentage of participants |                     |                      |                      |                      |
| number (confidence interval 90%)  | 31.0 (19.4 to 44.6) | 49.2 (37.8 to 60.5)  | 62.3 (51.0 to 72.7)  | 20.0 (10.4 to 33.2)  |

| End point values                  | NSCLC 300 mg/q3w     |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 59                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| number (confidence interval 90%)  | 35.6 (25.2 to 47.1)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Progression Free Survival as per Investigator based on RECIST v1.1

|                 |  |
|-----------------|--|
| End point title | Phase II: Progression Free Survival as per Investigator based on RECIST v1.1 <sup>[24]</sup> |
|-----------------|--|

End point description:

PFS is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. PFS is per Kaplan-Meier estimates.

RECIST criteria, published in February 2000 by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group, is a Response evaluation criteria in solid tumors is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

61 months

Notes:

[24] - 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: No statistical analysis planned

| End point values                  | ATC 400 mg/q4w   | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-----------------------------------|------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group  | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed       | 42               | 59                   | 61                   | 40                   |
| Units: Percentage of participants |                  |                      |                      |                      |
| median (confidence interval 90%)  | 1.7 (1.4 to 1.9) | 2.7 (1.9 to 5.4)     | 4.7 (3.5 to 5.6)     | 1.7 (1.7 to 1.8)     |

| End point values                  | NSCLC 300 mg/q3w     |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 59                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| median (confidence interval 90%)  | 1.9 (1.8 to 2.1)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Duration of response (DOR) as per Investigator based on RECIST v1.1

|                 |   |
|-----------------|---|
| End point title | Phase II: Duration of response (DOR) as per Investigator based on RECIST v1.1 <sup>[25]</sup> |
|-----------------|---|

End point description:

DOR is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented.

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

PD = progression <= start of treatment (and not qualifying for CR, PR or SD).

SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

RECIST criteria is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

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

End point timeframe:

61 months

Notes:

[25] - 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: No statistical analysis planned

| End point values                 | ATC 400 mg/q4w    | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | NSCLC 300 mg/q3w     |
|----------------------------------|-------------------|----------------------|----------------------|----------------------|
| Subject group type               | Reporting group   | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed      | 8                 | 9                    | 17                   | 4                    |
| Units: months                    |                   |                      |                      |                      |
| median (confidence interval 90%) | 22.8 (5.7 to 999) | 5.6 (3.9 to 16.6)    | 32.0 (11.1 to 999)   | 10.9 (3.7 to 999)    |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase II: Overall response rate (ORR) as per Investigator based on irRC

|                 |   |
|-----------------|---|
| End point title | Phase II: Overall response rate (ORR) as per Investigator based on irRC <sup>[26]</sup> |
|-----------------|---|

End point description:

ORR is the percentage of participants with a best overall response CR or PR as per irRC.

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required.

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

The immune-related response criteria (irRC) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug.

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

End point timeframe:

61 months

Notes:

[26] - 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: No statistical analysis planned

| End point values                  | ATC 400 mg/q4w      | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-----------------------------------|---------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group     | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed       | 42                  | 59                   | 61                   | 40                   |
| Units: Percentage of participants |                     |                      |                      |                      |
| number (confidence interval 90%)  | 23.8 (13.5 to 37.0) | 18.6 (10.8 to 29.0)  | 31.1 (21.5 to 42.3)  | 0.0 (0.0 to 7.2)     |

| End point values                  | NSCLC 300 mg/q3w     |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 59                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| number (confidence interval 90%)  | 8.5 (3.4 to 17.0)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Disease Control rate (DCR) as per Investigator based on irRC

|                 |  |
|-----------------|--|
| End point title | Phase II: Disease Control rate (DCR) as per Investigator based on irRC <sup>[27]</sup> |
|-----------------|--|

End point description:

DCR is the percentage of patients with a best overall response of CR or PR or stable disease (SD).

CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.

SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

The immune-related response criteria (irRC) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug.

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

End point timeframe:

61 months

Notes:

[27] - 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: No statistical analysis planned

| End point values                  | ATC 400 mg/q4w      | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-----------------------------------|---------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group     | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed       | 42                  | 59                   | 61                   | 40                   |
| Units: Percentage of participants |                     |                      |                      |                      |
| number (confidence interval 90%)  | 35.7 (23.5 to 49.5) | 55.9 (44.4 to 67.0)  | 67.2 (56.0 to 77.1)  | 22.5 (12.3 to 36.0)  |

| End point values                  | NSCLC 300 mg/q3w     |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 59                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| number (confidence interval 90%)  | 39.0 (28.3 to 50.5)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Progression Free Survival (PFS) per irRC

|                 |  |
|-----------------|--|
| End point title | Phase II: Progression Free Survival (PFS) per irRC <sup>[28]</sup> |
|-----------------|--|

End point description:

PFS is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. PFS is per Kaplan-Meier estimates.

The immune-related response criteria (irRC) is a set of published rules that define when tumors in

cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug.

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

End point timeframe:

61 months

Notes:

[28] - 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: No statistical analysis planned

| End point values                  | ATC 400 mg/q4w   | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | TNBC 400 mg/q4w      |
|-----------------------------------|------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group  | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed       | 42               | 59                   | 61                   | 40                   |
| Units: Percentage of participants |                  |                      |                      |                      |
| median (confidence interval 90%)  | 1.7 (1.4 to 1.9) | 3.7 (2.6 to 7.1)     | 5.4 (3.7 to 6.5)     | 1.8 (1.7 to 1.8)     |

| End point values                  | NSCLC 300 mg/q3w     |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 59                   |  |  |  |
| Units: Percentage of participants |                      |  |  |  |
| median (confidence interval 90%)  | 2.0 (1.8 to 2.2)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Duration of response (DOR) per irRC

|                 |   |
|-----------------|---|
| End point title | Phase II: Duration of response (DOR) per irRC <sup>[29]</sup> |
|-----------------|---|

End point description:

DOR: measured from time measurement criteria are met for CR or PR (whichever status is recorded first) until first date that recurrence or PD is objectively documented CR: at least 2 determinations of CR at least 4 weeks apart before progression where confirmation required or 1 determination of CR prior to progression where confirmation not required PR: at least 1 determination of PR or better at least 4 weeks apart before progression (& not qualifying for a CR) where confirmation required or 1 determination of PR prior to progression where confirmation not required PD: progression ≤ start of treatment (& not qualifying for CR, PR or SD) SD: at least 1 SD assessment (or better) > 6 weeks after randomization/start of treatment (& not qualifying for CR or PR)

irRC is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment, where the compound being evaluated is an immuno-oncology drug

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

End point timeframe:

61 months

Notes:

[29] - 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: No statistical analysis planned

| End point values                 | ATC 400 mg/q4w    | NSCLC 400 mg/q4w     | Melanoma 400 mg/q4w  | NSCLC 300 mg/q3w     |
|----------------------------------|-------------------|----------------------|----------------------|----------------------|
| Subject group type               | Reporting group   | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed      | 10                | 11                   | 19                   | 5                    |
| Units: months                    |                   |                      |                      |                      |
| median (confidence interval 90%) | 22.1 (3.8 to 999) | 5.6 (5.3 to 16.6)    | 32.0 (15.6 to 999)   | 10.9 (3.7 to 999)    |

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: All Collected Deaths

|                 |                      |
|-----------------|----------------------|
| End point title | All Collected Deaths |
|-----------------|----------------------|

End point description:

On treatment deaths were collected from the start of treatment up to 30 days after study drug discontinuation, for a maximum duration of 114.3 weeks for Phase I part (treatment duration ranged from 2 to 110.3 weeks) and a maximum duration of 194.9 weeks for Phase II part (treatment duration ranged from 0.6 to 190.9 weeks).

Deaths post treatment survival follow up were collected after the on-treatment period up to approx. 63 months.

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

On treatment deaths: approx. 114.3 weeks (Phase I) & 194.9 weeks (phase II), all deaths: approx. 63 months

| End point values            | Phase 1 Part         | Phase 2 Part         |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 58                   | 261                  |  |  |
| Units: Participants         |                      |                      |  |  |
| On-treatment deaths         | 8                    | 35                   |  |  |
| Total deaths                | 37                   | 177                  |  |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On treatment deaths were collected from first patient first treatment up to 30 days after study drug discontinuation, for a maximum duration of 114.3 weeks for the Part I phase and for a maximum duration of 194.9 weeks for the Phase II part.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | 1 mg/kg q2w |
|-----------------------|-------------|

Reporting group description:

Phase I Dose escalation cohort patients who took PDR001 1 mg/kg q2w

|                       |             |
|-----------------------|-------------|
| Reporting group title | 3 mg/kg q2w |
|-----------------------|-------------|

Reporting group description:

Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q2w

|                       |              |
|-----------------------|--------------|
| Reporting group title | 10 mg/kg q2w |
|-----------------------|--------------|

Reporting group description:

Phase I Dose escalation cohort patients who took PRD001 10 mg/kg q2w

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | All Phase I q2w |
|-----------------------|-----------------|

Reporting group description:

Phase I dose Cohorts - All patients in Phase I who took PDR001 q2w

|                       |             |
|-----------------------|-------------|
| Reporting group title | 3 mg/kg q4w |
|-----------------------|-------------|

Reporting group description:

Phase I Dose escalation cohort patients who took PRD001 3 mg/kg q4w

|                       |             |
|-----------------------|-------------|
| Reporting group title | 5 mg/kg q4w |
|-----------------------|-------------|

Reporting group description:

Phase I Dose escalation cohort patients who took PRD001 5 mg/kg q4w

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | All phase I q4w |
|-----------------------|-----------------|

Reporting group description:

Phase I dose Cohorts - All patients in Phase I who took PDR001 q4w

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | All phase I patients |
|-----------------------|----------------------|

Reporting group description:

All patients in Phase I regardless of how they took PDR001

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | NSCLC 400mg/q4w |
|-----------------------|-----------------|

Reporting group description:

Phase II: non-small cell cancer patients who took PDR001 400 mg/q4w

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Melanoma 400mg/q4w |
|-----------------------|--------------------|

Reporting group description:

Phase II: Melanoma patients who took PDR001 400 mg/q4w

|                       |                |
|-----------------------|----------------|
| Reporting group title | TNBC 400mg/q4w |
|-----------------------|----------------|

Reporting group description:

Phase II: Triple negative breast cancer (TNBC) patients who took PDR001 400 mg/q4w

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | NSCLC 300mg/q3w |
|-----------------------|-----------------|

Reporting group description:

Phase II: non-small cell cancer patients who took PDR001 300 mg/q3w

|                       |                |
|-----------------------|----------------|
| Reporting group title | ATC 400 mg/q4w |
|-----------------------|----------------|

Reporting group description:

Patients in Phase II with anaplastic thyroid cancer (ATC) who took PDR001 400 mg/q4w

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | All phase II patients |
|-----------------------|-----------------------|

Reporting group description:

All patients in Phase II regardless of how they took PDR001

| Serious adverse events  | 1 mg/kg q2w     | 3 mg/kg q2w     | 10 mg/kg q2w    |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events                   |                 |                 |                 |
| subjects affected / exposed   | 9 / 16 (56.25%) | 7 / 15 (46.67%) | 4 / 11 (36.36%) |
| number of deaths (all causes)                                       | 2               | 2               | 1               |
| number of deaths resulting from adverse events                      | 0               | 0               | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| Bladder cancer  |                 |                 |                 |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (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   | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (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           |
| Intracranial tumour haemorrhage                                     |                 |                 |                 |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (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 central nervous system                                |                 |                 |                 |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (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           |
| Second primary malignancy   |                 |                 |                 |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (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           |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Tumour haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Tumour inflammation                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Tumour pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                              |                |                |                |
| Embolism  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Lymphoedema                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Lymphorrhoea                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Superior vena cava syndrome                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| General disorders and administration            |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| site conditions                                 |                |                |                |
| Asthenia  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Complication of device insertion                |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Fatigue   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Non-cardiac chest pain                          |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Oedema peripheral                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Pain  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 swelling                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 system disorders                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Anaphylactic reaction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Sarcoidosis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Reproductive system and breast disorders        |                |                |                |
| Pelvic pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 |                |                |                |
| Acute respiratory distress syndrome             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Bronchial obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Cough   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Obstructive airways disorder                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Pharyngeal haemorrhage                          |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia aspiration                            |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Pneumonitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Pneumothorax                                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 distress                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| Tracheal stenosis                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                           |                |                |                |
| Confusional state                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                                  |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Blood bilirubin increased<br>subjects affected / exposed | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural<br>complications        |                |                |                |
| Hip fracture   |                |                |                |
| subjects affected / exposed                              | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Overdose   |                |                |                |
| subjects affected / exposed                              | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Thoracic vertebral fracture                              |                |                |                |
| subjects affected / exposed                              | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Tracheal obstruction                                     |                |                |                |
| subjects affected / exposed                              | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Wound dehiscence   |                |                |                |
| subjects affected / exposed                              | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders  |                |                |                |
| Acute coronary syndrome                                  |                |                |                |
| subjects affected / exposed                              | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                              |                |                |                |
| subjects affected / exposed                              | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Arrhythmia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Atrial flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Coronary artery stenosis                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Tachycardia                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                        |                |                |                |
| Ataxia  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Carotid artery occlusion                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Central nervous system lesion                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Cognitive disorder                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Encephalopathy                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Facial paralysis                                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Hydrocephalus                                   |                |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%) | 0 / 11 (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          |
| Intracranial pressure increased                 |                 |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%) | 0 / 11 (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          |
| Ischaemic stroke                                |                 |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%) | 0 / 11 (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          |
| Seizure   |                 |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%) | 0 / 11 (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 cord compression                         |                 |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) | 0 / 11 (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          |
| Blood and lymphatic system disorders            |                 |                |                |
| Anaemia   |                 |                |                |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Lymphadenopathy                                 |                 |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Thrombocytopenia                                |                 |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) | 0 / 11 (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          |
| Eye disorders                                   |                 |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| Diplopia  |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 0 / 11 (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 distension                            |                |                 |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Abdominal pain                                  |                |                 |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 2 / 15 (13.33%) | 0 / 11 (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          |
| Autoimmune colitis                              |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Constipation                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 0 / 11 (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                     | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (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          |
| Dysphagia                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Gastric ulcer                                   |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (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          |
| Gastrointestinal haemorrhage                    |                |                 |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Ileus   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Melaena   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Rectal haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Bile duct obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Hepatic failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |                |                |                |
| Dermatitis atopic                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     |                |                |                |
| Renal failure                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Fistula   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Groin pain                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Musculoskeletal chest pain                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Sjogren's syndrome                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     |                |                |                |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 difficile infection                 |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Empyema   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Gastroenteritis viral                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Localised infection                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 1 / 16 (6.25%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Postoperative wound infection                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 tract infection                         |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Diabetic ketoacidosis                           |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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          |
| Failure to thrive                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (6.25%) | 1 / 15 (6.67%) | 0 / 11 (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          |
| Hyperkalaemia                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (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                     | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (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          |

| <b>Serious adverse events</b>                                       | All Phase I q2w  | 3 mg/kg q4w    | 5 mg/kg q4w     |
|---|------------------|----------------|-----------------|
| Total subjects affected by serious adverse events                   |                  |                |                 |
| subjects affected / exposed   | 20 / 42 (47.62%) | 2 / 6 (33.33%) | 2 / 10 (20.00%) |
| number of deaths (all causes)                                       | 5                | 1              | 2               |
| number of deaths resulting from adverse events                      | 0                | 0              | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                |                 |
| Bladder cancer  |                  |                |                 |
| subjects affected / exposed   | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 0 / 10 (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   | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 0 / 10 (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           |
| Intracranial tumour haemorrhage                                     |                  |                |                 |
| subjects affected / exposed   | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 0 / 10 (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 central nervous system            |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Second primary malignancy                       |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Tumour haemorrhage                              |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Tumour inflammation                             |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Tumour pain                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                              |                |               |                |
| Embolism  |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Lymphoedema                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |

|  |                |               |                |
|--|----------------|---------------|----------------|
| Lymphorrhoea   |                |               |                |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Superior vena cava syndrome                          |                |               |                |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| General disorders and administration site conditions |                |               |                |
| Asthenia   |                |               |                |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Complication of device insertion                     |                |               |                |
| subjects affected / exposed                          | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Fatigue  |                |               |                |
| subjects affected / exposed                          | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Non-cardiac chest pain                               |                |               |                |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Oedema peripheral                                    |                |               |                |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Pain   |                |               |                |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 swelling                             |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Pyrexia   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 system disorders                         |                |               |                |
| Anaphylactic reaction                           |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Sarcoidosis                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Reproductive system and breast disorders        |                |               |                |
| Pelvic pain                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 |                |               |                |
| Acute respiratory distress syndrome             |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Bronchial obstruction                           |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Cough   |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Haemoptysis                                     |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Hypoxia   |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Obstructive airways disorder                    |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Pharyngeal haemorrhage                          |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Pleural effusion                                |                |               |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pneumonia aspiration                            |                |               |                 |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Pneumonitis                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Pneumothorax                                    |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 embolism                              |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 distress                            |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 failure                             |                |               |                |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 2          | 0 / 0         | 0 / 0          |
| Tracheal stenosis                               |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                           |                |               |                |
| Confusional state                               |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Depression                                      |                |               |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (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          |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 6 (16.67%) | 0 / 10 (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          |
| Investigations                                  |                |                |                |
| Blood bilirubin increased                       |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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  |                |                |                |
| Hip fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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          |
| Overdose  |                |                |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (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          |
| Thoracic vertebral fracture                     |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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          |
| Wound dehiscence                                |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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                               |                |               |                |
| Acute coronary syndrome                         |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 myocardial infarction                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Arrhythmia                                      |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Atrial fibrillation                             |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Atrial flutter                                  |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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 arrest                                  |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Coronary artery stenosis                        |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Tachycardia                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                        |                |               |                |
| Ataxia  |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Carotid artery occlusion                        |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Central nervous system lesion                   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Cognitive disorder                              |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Encephalopathy                                  |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Facial paralysis                                |                |               |                |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Haemorrhage intracranial                        |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Hydrocephalus                                   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Intracranial pressure increased                 |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Ischaemic stroke                                |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Seizure   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 cord compression                         |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Blood and lymphatic system disorders            |                |               |                |
| Anaemia   |                |               |                |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Lymphadenopathy                                 |                |               |                |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Thrombocytopenia                                |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Eye disorders                                   |                |               |                |
| Diplopia  |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 distension                            |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Abdominal pain                                  |                |               |                |
| subjects affected / exposed                     | 3 / 42 (7.14%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Autoimmune colitis                              |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Constipation                                    |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Dysphagia                                       |                |               |                |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastric ulcer                                   |                |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal haemorrhage                    |                |                |                 |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 0 / 6 (0.00%)  | 0 / 10 (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           |
| Ileus   |                |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (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           |
| Intestinal obstruction                          |                |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 6 (16.67%) | 0 / 10 (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           |
| Melaena   |                |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Rectal haemorrhage                              |                |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Vomiting  |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Hepatobiliary disorders                         |                |               |                 |
| Autoimmune hepatitis                            |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Bile duct obstruction                           |                |               |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Hepatic failure                                 |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |                |               |                 |
| Dermatitis atopic                               |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     |                |               |                 |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Renal failure                                   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Musculoskeletal and connective tissue disorders |                |               |                |
| Back pain                                       |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Fistula   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Groin pain                                      |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Musculoskeletal chest pain                      |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Pain in extremity                               |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Sjogren's syndrome                              |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     |                |               |                |
| Bacteraemia                                     |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 difficile infection                 |                |               |                |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Empyema   |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Gastroenteritis viral                           |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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          |
| Localised infection                             |                |               |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0         | 0 / 0           |
| Postoperative wound infection                   |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Sepsis  |                |               |                 |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0         | 0 / 0           |
| Septic shock                                    |                |               |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 0 / 10 (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 tract infection                         |                |               |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Metabolism and nutrition disorders              |                |               |                 |
| Dehydration                                     |                |               |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Diabetic ketoacidosis                           |                |               |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (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           |
| Failure to thrive                               |                |               |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Hypercalcaemia</b>                           |                |                |                 |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 1 / 6 (16.67%) | 0 / 10 (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           |
| <b>Hyperkalaemia</b>                            |                |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Hypoglycaemia</b>                            |                |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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           |
| <b>Hypokalaemia</b>                             |                |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (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           |
| <b>Hyponatraemia</b>                            |                |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

| <b>Serious adverse events</b>  | All phase I q4w | All phase I patients | NSCLC 400mg/q4w  |
|--|-----------------|----------------------|------------------|
| Total subjects affected by serious adverse events                          |                 |                      |                  |
| subjects affected / exposed  | 4 / 16 (25.00%) | 24 / 58 (41.38%)     | 27 / 59 (45.76%) |
| number of deaths (all causes)  | 3               | 8                    | 4                |
| number of deaths resulting from adverse events                             | 0               | 0                    | 0                |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                 |                      |                  |
| <b>Bladder cancer</b>  |                 |                      |                  |
| subjects affected / exposed  | 0 / 16 (0.00%)  | 0 / 58 (0.00%)       | 0 / 59 (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                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intracranial tumour haemorrhage                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 central nervous system            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Second primary malignancy                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Tumour haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Tumour inflammation                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Tumour pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                              |                |                |                |
| Embolism  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Hypotension  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Lymphoedema  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Lymphorrhoea   |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Superior vena cava syndrome                          |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| General disorders and administration site conditions |                |                |                |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Complication of device insertion                     |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Fatigue  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Non-cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Oedema peripheral                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Pain  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 swelling                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 system disorders                         |                |                |                |
| Anaphylactic reaction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Sarcoidosis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Reproductive system and breast disorders        |                |                |                |
| Pelvic pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 |                |                |                |
| Acute respiratory distress syndrome             |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Bronchial obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Chronic obstructive pulmonary disease           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Cough   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 1 / 16 (6.25%) | 2 / 58 (3.45%) | 3 / 59 (5.08%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Haemoptysis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Obstructive airways disorder                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Pharyngeal haemorrhage                          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 2 / 58 (3.45%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia aspiration                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 0 / 59 (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          |
| Pneumonitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory distress                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 1          |
| Tracheal stenosis                               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                           |                |                |                |
| Confusional state                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Investigations                                  |                |                |                |
| Blood bilirubin increased                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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  |                |                |                |
| Hip fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Overdose  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Thoracic vertebral fracture                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Wound dehiscence                                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                               |                |                |                |
| Acute coronary syndrome                         |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Arrhythmia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 3 / 59 (5.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Coronary artery stenosis                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tachycardia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                        |                |                |                |
| Ataxia  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Carotid artery occlusion                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Central nervous system lesion                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Cognitive disorder                              |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Encephalopathy                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Facial paralysis                                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Hydrocephalus                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Intracranial pressure increased                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 cord compression                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 3 / 59 (5.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| <b>Blood and lymphatic system disorders</b>     |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lymphadenopathy                                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| <b>Eye disorders</b>                            |                |                |                |
| Diplopia  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| Abdominal distension                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 3 / 58 (5.17%) | 0 / 59 (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          |
| Autoimmune colitis                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Constipation                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Dysphagia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 0 / 59 (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          |
| Ileus   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Melaena   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 1 / 16 (6.25%) | 2 / 58 (3.45%) | 0 / 59 (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          |
| Rectal haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Autoimmune hepatitis                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Bile duct obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Hepatic failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |                |                |                |
| Dermatitis atopic                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal failure                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                |                |                |
| Adrenal insufficiency                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bone pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Fistula   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Groin pain                                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Musculoskeletal chest pain                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Sjogren's syndrome                              |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     |                |                |                |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 difficile infection                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Empyema   |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Gastroenteritis viral                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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          |
| Localised infection                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 3 / 59 (5.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 5          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Postoperative wound infection                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 2 / 58 (3.45%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diabetic ketoacidosis                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Failure to thrive                               |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 0 / 59 (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          |
| Hypercalcaemia                                  |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 3 / 58 (5.17%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 2 / 58 (3.45%) | 0 / 59 (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          |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 0 / 59 (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 / 16 (0.00%) | 0 / 58 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 16 (6.25%) | 2 / 58 (3.45%) | 0 / 59 (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          |

| <b>Serious adverse events</b>                                       | Melanoma<br>400mg/q4w | TNBC 400mg/q4w   | NSCLC 300mg/q3w  |
|---|-----------------------|------------------|------------------|
| Total subjects affected by serious adverse events                   |                       |                  |                  |
| subjects affected / exposed   | 22 / 61 (36.07%)      | 18 / 40 (45.00%) | 37 / 59 (62.71%) |
| number of deaths (all causes)                                       | 4                     | 4                | 12               |
| number of deaths resulting from adverse events                      | 0                     | 0                | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                  |                  |
| Bladder cancer  |                       |                  |                  |
| subjects affected / exposed   | 0 / 61 (0.00%)        | 0 / 40 (0.00%)   | 1 / 59 (1.69%)   |
| occurrences causally related to treatment / all                     | 0 / 0                 | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0            | 0 / 0            |
| Cancer pain   |                       |                  |                  |
| subjects affected / exposed   | 0 / 61 (0.00%)        | 0 / 40 (0.00%)   | 0 / 59 (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            |
| Intracranial tumour haemorrhage                                     |                       |                  |                  |
| subjects affected / exposed   | 1 / 61 (1.64%)        | 0 / 40 (0.00%)   | 0 / 59 (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            |
| Metastases to central nervous system                                |                       |                  |                  |
| subjects affected / exposed   | 0 / 61 (0.00%)        | 0 / 40 (0.00%)   | 0 / 59 (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            |
| Second primary malignancy   |                       |                  |                  |
| subjects affected / exposed   | 1 / 61 (1.64%)        | 0 / 40 (0.00%)   | 0 / 59 (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 haemorrhage  |                       |                  |                  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 2 / 61 (3.28%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Tumour inflammation                                  |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Tumour pain  |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 2 / 40 (5.00%) | 0 / 59 (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          |
| Vascular disorders                                   |                |                |                |
| Embolism   |                |                |                |
| subjects affected / exposed                          | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Hypotension  |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Lymphoedema  |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Lymphorrhoea   |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Superior vena cava syndrome                          |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Asthenia  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Complication of device insertion                |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Fatigue   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Non-cardiac chest pain                          |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oedema peripheral                               |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Peripheral swelling                             |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 1 / 40 (2.50%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Anaphylactic reaction                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sarcoidosis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Reproductive system and breast disorders        |                |                |                |
| Pelvic pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Acute respiratory distress syndrome             |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Bronchial obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Cough   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea  |                |                |                |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 61 (1.64%) | 3 / 40 (7.50%)  | 7 / 59 (11.86%) |
| occurrences causally related to treatment / all | 0 / 1          | 2 / 4           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 5           |
| Haemoptysis                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 2 / 59 (3.39%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Hypoxia   |                |                 |                 |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (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           |
| Obstructive airways disorder                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (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           |
| Pharyngeal haemorrhage                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (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           |
| Pleural effusion                                |                |                 |                 |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 5 / 40 (12.50%) | 2 / 59 (3.39%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Pneumonia aspiration                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (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                     | 1 / 61 (1.64%) | 0 / 40 (0.00%)  | 1 / 59 (1.69%)  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumothorax                                    |                |                 |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 distress                            |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Tracheal stenosis                               |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                           |                |                |                |
| Confusional state                               |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                                  |                |                |                |



|  |                |                |                |
|--|----------------|----------------|----------------|
| Blood bilirubin increased<br>subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural<br>complications        |                |                |                |
| Hip fracture   |                |                |                |
| subjects affected / exposed                              | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Overdose   |                |                |                |
| subjects affected / exposed                              | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Thoracic vertebral fracture                              |                |                |                |
| subjects affected / exposed                              | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Tracheal obstruction                                     |                |                |                |
| subjects affected / exposed                              | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Wound dehiscence   |                |                |                |
| subjects affected / exposed                              | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to<br>treatment / all       | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders  |                |                |                |
| Acute coronary syndrome                                  |                |                |                |
| subjects affected / exposed                              | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                              |                |                |                |
| subjects affected / exposed                              | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to<br>treatment / all       | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Arrhythmia                                      |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Atrial flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 / 61 (0.00%) | 0 / 40 (0.00%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 2          |
| Cardiac tamponade                               |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery stenosis                        |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericardial effusion                            |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Tachycardia                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Ataxia  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Carotid artery occlusion                        |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Central nervous system lesion                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cognitive disorder                              |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Encephalopathy                                  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Facial paralysis                                |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Hydrocephalus                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intracranial pressure increased                 |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal cord compression                         |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Lymphadenopathy                                 |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Eye disorders                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Diplopia  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal distension                            |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                                  |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 2 / 40 (5.00%) | 0 / 59 (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          |
| Autoimmune colitis                              |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dysphagia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric ulcer                                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 haemorrhage                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Ileus   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Melaena   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Rectal haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Autoimmune hepatitis                            |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Bile duct obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Hepatic failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Hyperbilirubinaemia                             |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Jaundice  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Dermatitis atopic                               |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     |                |                |                |
| Renal failure                                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 4 / 59 (6.78%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bone pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Fistula   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Groin pain                                      |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Musculoskeletal chest pain                      |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Sjogren's syndrome                              |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Infections and infestations                     |                |                |                |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 2 / 61 (3.28%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Clostridium difficile infection                 |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Empyema   |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Gastroenteritis viral                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Localised infection                             |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 5 / 59 (8.47%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 6          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Postoperative wound infection                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory tract infection                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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 tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 2 / 40 (5.00%) | 0 / 59 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Diabetic ketoacidosis                           |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Failure to thrive                               |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Hypercalcaemia                                  |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (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          |
| Hypokalaemia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |
| Hyponatraemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (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          |

| <b>Serious adverse events</b>                                       | ATC 400 mg/q4w   | All phase II patients |  |
|---|------------------|-----------------------|--|
| Total subjects affected by serious adverse events                   |                  |                       |  |
| subjects affected / exposed   | 22 / 42 (52.38%) | 126 / 261 (48.28%)    |  |
| number of deaths (all causes)                                       | 11               | 35                    |  |
| number of deaths resulting from adverse events                      | 0                | 0                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                       |  |
| Bladder cancer  |                  |                       |  |
| subjects affected / exposed   | 0 / 42 (0.00%)   | 1 / 261 (0.38%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1                 |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0                 |  |
| Cancer pain   |                  |                       |  |
| subjects affected / exposed   | 0 / 42 (0.00%)   | 1 / 261 (0.38%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1                 |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0                 |  |
| Intracranial tumour haemorrhage                                     |                  |                       |  |
| subjects affected / exposed   | 1 / 42 (2.38%)   | 2 / 261 (0.77%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 2                 |  |
| deaths causally related to treatment / all                          | 0 / 1            | 0 / 2                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Metastases to central nervous system            |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Second primary malignancy                       |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tumour haemorrhage                              |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tumour inflammation                             |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tumour pain                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vascular disorders                              |                |                 |  |
| Embolism  |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Hypotension                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lymphoedema                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Lymphorrhoea   |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Superior vena cava syndrome                          |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Asthenia   |                |                 |  |
| subjects affected / exposed                          | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Complication of device insertion                     |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Fatigue  |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Non-cardiac chest pain                               |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Oedema peripheral                                    |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Pain   |                |                 |  |
| subjects affected / exposed                          | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Peripheral swelling                             |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pyrexia   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 4 / 261 (1.53%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Immune system disorders                         |                |                 |  |
| Anaphylactic reaction                           |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sarcoidosis                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Reproductive system and breast disorders        |                |                 |  |
| Pelvic pain                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Acute respiratory distress syndrome             |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Bronchial obstruction                           |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                |                 |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| Cough   |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Dyspnoea  |                |                  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 16 / 261 (6.13%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 2 / 17           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 7            |  |
| Haemoptysis                                     |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| Hypoxia   |                |                  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Obstructive airways disorder                    |                |                  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1            |  |
| Pharyngeal haemorrhage                          |                |                  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1            |  |
| Pleural effusion                                |                |                  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 11 / 261 (4.21%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| Pneumonia aspiration                            |                |                  |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonitis                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 4 / 261 (1.53%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumothorax                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary embolism                              |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory distress                            |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory failure                             |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| Tracheal stenosis                               |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Psychiatric disorders                           |                |                 |  |
| Confusional state                               |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Depression                                      |                |                 |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Mental status changes                           |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Investigations                                  |                |                 |  |
| Blood bilirubin increased                       |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                |                 |  |
| Hip fracture                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Overdose  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thoracic vertebral fracture                     |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tracheal obstruction                            |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Wound dehiscence                                |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Cardiac disorders                               |                |                 |  |
| Acute coronary syndrome                         |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute myocardial infarction                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Arrhythmia                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrial fibrillation                             |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 4 / 261 (1.53%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrial flutter                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac arrest                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| Cardiac tamponade                               |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Coronary artery stenosis                        |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Myocardial infarction                           |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pericardial effusion                            |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Tachycardia                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                        |                |                 |  |
| Ataxia  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Carotid artery occlusion                        |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Central nervous system lesion                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cognitive disorder                              |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Encephalopathy                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Facial paralysis                                |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haemorrhage intracranial                        |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hydrocephalus                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Intracranial pressure increased                 |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Ischaemic stroke                                |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Seizure   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Spinal cord compression                         |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Blood and lymphatic system disorders            |                |                 |  |
| Anaemia   |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lymphadenopathy                                 |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thrombocytopenia                                |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Eye disorders                                   |                |                 |  |
| Diplopia  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Abdominal distension                            |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Abdominal pain                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Autoimmune colitis                              |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Constipation                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Diarrhoea                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dysphagia                                       |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 42 (4.76%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1           |  |
| Gastric ulcer                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Ileus   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Intestinal obstruction                          |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Melaena   |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nausea  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Rectal haemorrhage                              |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vomiting  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hepatobiliary disorders                         |                |                 |  |
| Autoimmune hepatitis                            |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Bile duct obstruction                           |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hepatic failure                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Hyperbilirubinaemia                             |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Jaundice  |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                |                 |  |
| Dermatitis atopic                               |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Renal failure                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Endocrine disorders                             |                |                 |  |
| Adrenal insufficiency                           |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Back pain                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 6 / 261 (2.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Bone pain                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Fistula   |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Groin pain                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal chest pain                      |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pain in extremity                               |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| Sjogren's syndrome                              |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Bacteraemia                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Bronchitis                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cellulitis                                      |                |                 |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 4 / 261 (1.53%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Clostridium difficile infection                 |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Empyema   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastroenteritis viral                           |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Localised infection                             |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonia                                       |                |                 |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 3 / 42 (7.14%) | 11 / 261 (4.21%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 1 / 14           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| Postoperative wound infection                   |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Respiratory tract infection                     |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| Sepsis  |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 3 / 261 (1.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| Septic shock                                    |                |                  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 2 / 261 (0.77%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Urinary tract infection                         |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Metabolism and nutrition disorders              |                |                  |  |
| Dehydration                                     |                |                  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 3 / 261 (1.15%)  |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Diabetic ketoacidosis                           |                |                  |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Failure to thrive                               |                |                  |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Hypercalcaemia                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 3 / 261 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hyperkalaemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypoglycaemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypokalaemia                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hyponatraemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                   | 1 mg/kg q2w       | 3 mg/kg q2w       | 10 mg/kg q2w      |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events               |                   |                   |                   |
| subjects affected / exposed   | 16 / 16 (100.00%) | 15 / 15 (100.00%) | 11 / 11 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Cancer pain   |                   |                   |                   |
| subjects affected / exposed   | 0 / 16 (0.00%)    | 0 / 15 (0.00%)    | 0 / 11 (0.00%)    |
| occurrences (all)   | 0                 | 0                 | 0                 |
| Tumour haemorrhage  |                   |                   |                   |

|   |                        |                      |                      |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 2 / 16 (12.50%)<br>2   | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0  |
| Tumour pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0    | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0  |
| Vascular disorders<br>Deep vein thrombosis<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 16 (0.00%)<br>0    | 1 / 15 (6.67%)<br>1  | 0 / 11 (0.00%)<br>0  |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0    | 1 / 15 (6.67%)<br>1  | 0 / 11 (0.00%)<br>0  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1    | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0  |
| Lymphoedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0    | 0 / 15 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1    | 1 / 15 (6.67%)<br>1  | 0 / 11 (0.00%)<br>0  |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 2 / 16 (12.50%)<br>2   | 1 / 15 (6.67%)<br>1  | 1 / 11 (9.09%)<br>1  |
| Face oedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0    | 0 / 15 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 10 / 16 (62.50%)<br>10 | 3 / 15 (20.00%)<br>4 | 2 / 11 (18.18%)<br>2 |
| Inflammation<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1    | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0  |
| Influenza like illness  |                        |                      |                      |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed              | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 0               | 1               | 0               |
| Malaise                                  |                 |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 1               | 1               | 0               |
| Non-cardiac chest pain                   |                 |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%)  | 2 / 15 (13.33%) | 1 / 11 (9.09%)  |
| occurrences (all)                        | 1               | 2               | 1               |
| Oedema                                   |                 |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 0               | 1               | 0               |
| Oedema peripheral                        |                 |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%)  | 2 / 15 (13.33%) | 2 / 11 (18.18%) |
| occurrences (all)                        | 1               | 3               | 2               |
| Pain                                     |                 |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 0               | 1               | 0               |
| Peripheral swelling                      |                 |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 0               | 1               | 0               |
| Pyrexia                                  |                 |                 |                 |
| subjects affected / exposed              | 2 / 16 (12.50%) | 2 / 15 (13.33%) | 1 / 11 (9.09%)  |
| occurrences (all)                        | 4               | 2               | 1               |
| Swelling face                            |                 |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 1               | 0               | 0               |
| Immune system disorders                  |                 |                 |                 |
| Food allergy                             |                 |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 1               | 0               | 0               |
| Seasonal allergy                         |                 |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                        | 0               | 0               | 0               |
| Reproductive system and breast disorders |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pelvic pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Vulvovaginal pain                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Cough   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 16 (18.75%) | 4 / 15 (26.67%) | 0 / 11 (0.00%)  |
| occurrences (all)                               | 5               | 5               | 0               |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 5 / 16 (31.25%) | 7 / 15 (46.67%) | 2 / 11 (18.18%) |
| occurrences (all)                               | 9               | 9               | 3               |
| Dyspnoea exertional                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Haemoptysis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Hiccups   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Hypoxia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Oropharyngeal pain                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 3 / 16 (18.75%) | 1 / 15 (6.67%)  | 1 / 11 (9.09%)  |
| occurrences (all)                               | 4               | 1               | 1               |
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Productive cough                                |                 |                 |                 |

|                                    |                |                |                |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |
| Respiratory tract congestion       |                |                |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0              |
| Sinus congestion                   |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Tachypnoea                         |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Upper respiratory tract congestion |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Psychiatric disorders              |                |                |                |
| Affective disorder                 |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |
| Agitation                          |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |
| Anxiety                            |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Confusional state                  |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |
| Depression                         |                |                |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0              |
| Hallucination                      |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all)                  | 0              | 0              | 1              |
| Insomnia                           |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Investigations                              |                 |                 |                 |
| Alanine aminotransferase increased          |                 |                 |                 |
| subjects affected / exposed                 | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                           | 1               | 0               | 2               |
| Aspartate aminotransferase increased        |                 |                 |                 |
| subjects affected / exposed                 | 2 / 16 (12.50%) | 1 / 15 (6.67%)  | 2 / 11 (18.18%) |
| occurrences (all)                           | 2               | 2               | 2               |
| Bacterial test positive                     |                 |                 |                 |
| subjects affected / exposed                 | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 0               | 1               | 0               |
| Blood alkaline phosphatase increased        |                 |                 |                 |
| subjects affected / exposed                 | 3 / 16 (18.75%) | 2 / 15 (13.33%) | 0 / 11 (0.00%)  |
| occurrences (all)                           | 4               | 3               | 0               |
| Blood bilirubin increased                   |                 |                 |                 |
| subjects affected / exposed                 | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 1               | 1               | 0               |
| Blood creatinine decreased                  |                 |                 |                 |
| subjects affected / exposed                 | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 1               | 0               | 0               |
| Blood creatinine increased                  |                 |                 |                 |
| subjects affected / exposed                 | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 2               | 1               | 0               |
| Blood thyroid stimulating hormone increased |                 |                 |                 |
| subjects affected / exposed                 | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 0               | 0               | 0               |
| Gamma-glutamyltransferase increased         |                 |                 |                 |
| subjects affected / exposed                 | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 0               | 1               | 0               |
| Lymphocyte count decreased                  |                 |                 |                 |
| subjects affected / exposed                 | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                           | 0               | 0               | 3               |
| Transaminases increased                     |                 |                 |                 |
| subjects affected / exposed                 | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                           | 1               | 1               | 0               |
| Weight decreased                            |                 |                 |                 |



|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed                    | 4 / 16 (25.00%) | 2 / 15 (13.33%) | 1 / 11 (9.09%) |
| occurrences (all)                              | 4               | 2               | 1              |
| Weight increased                               |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 0               | 0               | 0              |
| White blood cell count decreased               |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)                              | 0               | 0               | 2              |
| Injury, poisoning and procedural complications |                 |                 |                |
| Contusion                                      |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 0               | 1               | 0              |
| Fall   |                 |                 |                |
| subjects affected / exposed                    | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 1               | 1               | 0              |
| Joint dislocation                              |                 |                 |                |
| subjects affected / exposed                    | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 1               | 0               | 0              |
| Ligament rupture                               |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 0               | 0               | 0              |
| Post-traumatic pain                            |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 0               | 0               | 0              |
| Procedural pain                                |                 |                 |                |
| subjects affected / exposed                    | 2 / 16 (12.50%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 3               | 1               | 0              |
| Wound complication                             |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                              | 0               | 0               | 0              |
| Cardiac disorders                              |                 |                 |                |
| Palpitations                                   |                 |                 |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)                              | 0               | 0               | 1              |
| Sinus tachycardia                              |                 |                 |                |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Tachycardia                 |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Nervous system disorders    |                 |                 |                |
| Amnesia                     |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Aphasia                     |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Dizziness                   |                 |                 |                |
| subjects affected / exposed | 4 / 16 (25.00%) | 6 / 15 (40.00%) | 0 / 11 (0.00%) |
| occurrences (all)           | 5               | 8               | 0              |
| Dysarthria                  |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Dysgeusia                   |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 15 (13.33%) | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 2               | 0              |
| Headache                    |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 4 / 15 (26.67%) | 1 / 11 (9.09%) |
| occurrences (all)           | 1               | 4               | 1              |
| Hypoaesthesia               |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 1               | 0              |
| Lethargy                    |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)           | 0               | 0               | 1              |
| Loss of consciousness       |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Neuralgia                   |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Neuropathy peripheral                  |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Paraesthesia                           |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                      | 0               | 0               | 1               |
| Paralysis                              |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                      | 0               | 0               | 1               |
| Peripheral sensory neuropathy          |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Presyncope                             |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 0               | 1               | 0               |
| Somnolence                             |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 0               | 0               | 0               |
| Taste disorder                         |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Tremor                                 |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                      | 1               | 0               | 1               |
| Blood and lymphatic system disorders   |                 |                 |                 |
| Anaemia                                |                 |                 |                 |
| subjects affected / exposed            | 5 / 16 (31.25%) | 7 / 15 (46.67%) | 2 / 11 (18.18%) |
| occurrences (all)                      | 10              | 11              | 3               |
| Disseminated intravascular coagulation |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 0               | 1               | 0               |
| Eosinophilia                           |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                      | 0               | 0               | 0               |
| Iron deficiency anaemia                |                 |                 |                 |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Leukocytosis                |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0              | 0               | 0              |
| Leukopenia                  |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Lymph node pain             |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Lymphopenia                 |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Neutropenia                 |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Thrombocytopenia            |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 15 (13.33%) | 0 / 11 (0.00%) |
| occurrences (all)           | 0              | 3               | 0              |
| Ear and labyrinth disorders |                |                 |                |
| Hypoacusis                  |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)           | 0              | 0               | 1              |
| Otorrhoea                   |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Vertigo                     |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Eye disorders               |                |                 |                |
| Periorbital oedema          |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Photopsia                   |                |                 |                |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Vision blurred              |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 1               | 1               | 0               |
| Gastrointestinal disorders  |                 |                 |                 |
| Abdominal discomfort        |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Abdominal distension        |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 1               | 1               | 1               |
| Abdominal pain              |                 |                 |                 |
| subjects affected / exposed | 3 / 16 (18.75%) | 2 / 15 (13.33%) | 2 / 11 (18.18%) |
| occurrences (all)           | 3               | 2               | 2               |
| Abdominal pain lower        |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Abdominal pain upper        |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 1               | 1               | 1               |
| Ascites                     |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Autoimmune colitis          |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Constipation                |                 |                 |                 |
| subjects affected / exposed | 5 / 16 (31.25%) | 5 / 15 (33.33%) | 0 / 11 (0.00%)  |
| occurrences (all)           | 5               | 8               | 0               |
| Diarrhoea                   |                 |                 |                 |
| subjects affected / exposed | 7 / 16 (43.75%) | 6 / 15 (40.00%) | 1 / 11 (9.09%)  |
| occurrences (all)           | 9               | 6               | 5               |
| Dry mouth                   |                 |                 |                 |
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 15 (6.67%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 3               | 1               | 1               |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| Dyspepsia                        |                 |                 |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                | 0               | 0               | 1               |
| Dysphagia                        |                 |                 |                 |
| subjects affected / exposed      | 1 / 16 (6.25%)  | 2 / 15 (13.33%) | 0 / 11 (0.00%)  |
| occurrences (all)                | 1               | 2               | 0               |
| Flatulence                       |                 |                 |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 0               | 1               | 0               |
| Gastrooesophageal reflux disease |                 |                 |                 |
| subjects affected / exposed      | 2 / 16 (12.50%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 2               | 1               | 0               |
| Mouth haemorrhage                |                 |                 |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                | 0               | 0               | 1               |
| Mouth ulceration                 |                 |                 |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 0               | 0               | 0               |
| Nausea                           |                 |                 |                 |
| subjects affected / exposed      | 7 / 16 (43.75%) | 4 / 15 (26.67%) | 3 / 11 (27.27%) |
| occurrences (all)                | 8               | 4               | 4               |
| Pancreatic duct dilatation       |                 |                 |                 |
| subjects affected / exposed      | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Rectal haemorrhage               |                 |                 |                 |
| subjects affected / exposed      | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Stomatitis                       |                 |                 |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 0               | 1               | 0               |
| Toothache                        |                 |                 |                 |
| subjects affected / exposed      | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Vomiting                         |                 |                 |                 |
| subjects affected / exposed      | 6 / 16 (37.50%) | 1 / 15 (6.67%)  | 3 / 11 (27.27%) |
| occurrences (all)                | 6               | 2               | 3               |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Hepatobiliary disorders                    |                |                |                |
| Cholecystitis                              |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 0              | 1              | 0              |
| Hyperbilirubinaemia                        |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Skin and subcutaneous tissue disorders     |                |                |                |
| Alopecia                                   |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Cold sweat                                 |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 0              | 1              | 0              |
| Dermatitis acneiform                       |                |                |                |
| subjects affected / exposed                | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Dermatitis contact                         |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 0              | 1              | 0              |
| Erythema                                   |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Hyperhidrosis                              |                |                |                |
| subjects affected / exposed                | 1 / 16 (6.25%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 1              | 1              | 0              |
| Lichen planus                              |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 15 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Night sweats                               |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 0              | 1              | 0              |
| Pain of skin                               |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 0 / 11 (0.00%) |
| occurrences (all)                          | 0              | 1              | 0              |
| Palmar-plantar erythrodysesthesia syndrome |                |                |                |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Papule                      |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Pruritus                    |                 |                 |                |
| subjects affected / exposed | 3 / 16 (18.75%) | 5 / 15 (33.33%) | 1 / 11 (9.09%) |
| occurrences (all)           | 4               | 5               | 1              |
| Rash                        |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 1               | 0              |
| Rash erythematous           |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Rash maculo-papular         |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 2 / 15 (13.33%) | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 2               | 0              |
| Skin ulcer                  |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)           | 0               | 0               | 1              |
| Vitiligo                    |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Renal and urinary disorders |                 |                 |                |
| Acute kidney injury         |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Azotaemia                   |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Dysuria                     |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Haematuria                  |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)           | 0               | 0               | 1              |



|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  | 0 / 11 (0.00%)<br>0 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 16 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)  | 3 / 16 (18.75%)<br>3 | 3 / 15 (20.00%)<br>3 | 1 / 11 (9.09%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 3 / 15 (20.00%)<br>3 | 1 / 11 (9.09%)<br>1 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 16 (12.50%)<br>2 | 2 / 15 (13.33%)<br>2 | 0 / 11 (0.00%)<br>0 |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 |
| Coccydynia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  | 1 / 15 (6.67%)<br>1  | 0 / 11 (0.00%)<br>0 |
| Groin pain  |                      |                      |                     |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 15 (13.33%) | 0 / 11 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0               |
| Limb discomfort             |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Muscle spasms               |                 |                 |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Muscular weakness           |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 1               | 1               | 1               |
| Musculoskeletal chest pain  |                 |                 |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 4               | 0               | 0               |
| Musculoskeletal pain        |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 2 / 11 (18.18%) |
| occurrences (all)           | 0               | 1               | 2               |
| Myalgia                     |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 2 / 15 (13.33%) | 0 / 11 (0.00%)  |
| occurrences (all)           | 1               | 2               | 0               |
| Neck pain                   |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 0               | 1               | 1               |
| Osteoarthritis              |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0               |
| Pain in extremity           |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 15 (13.33%) | 2 / 11 (18.18%) |
| occurrences (all)           | 0               | 2               | 2               |
| Pathological fracture       |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Infections and infestations |                 |                 |                 |
| Abdominal infection         |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0               |

|                               |                |                 |                |
|-------------------------------|----------------|-----------------|----------------|
| Acute sinusitis               |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 0               | 0              |
| Bacteraemia                   |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 1               | 0              |
| Fungal skin infection         |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 0              | 1               | 0              |
| Influenza                     |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 0              | 0               | 0              |
| Laryngitis bacterial          |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 0              | 1               | 0              |
| Nasopharyngitis               |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 0               | 0              |
| Oral candidiasis              |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 1               | 0              |
| Otitis media                  |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 0               | 0              |
| Peritonitis                   |                |                 |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 0              | 0               | 0              |
| Pneumonia                     |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 2 / 15 (13.33%) | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 2               | 0              |
| Postoperative wound infection |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 0               | 0              |
| Rhinitis                      |                |                 |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)             | 1              | 0               | 0              |

|                                    |                 |                 |                 |
|------------------------------------|-----------------|-----------------|-----------------|
| Sinusitis                          |                 |                 |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                  | 1               | 0               | 0               |
| Upper respiratory tract infection  |                 |                 |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%)  |
| occurrences (all)                  | 0               | 1               | 0               |
| Urinary tract infection            |                 |                 |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 3 / 15 (20.00%) | 0 / 11 (0.00%)  |
| occurrences (all)                  | 3               | 3               | 0               |
| Metabolism and nutrition disorders |                 |                 |                 |
| Cachexia                           |                 |                 |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                  | 1               | 0               | 0               |
| Decreased appetite                 |                 |                 |                 |
| subjects affected / exposed        | 5 / 16 (31.25%) | 1 / 15 (6.67%)  | 3 / 11 (27.27%) |
| occurrences (all)                  | 5               | 1               | 3               |
| Dehydration                        |                 |                 |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 2 / 15 (13.33%) | 1 / 11 (9.09%)  |
| occurrences (all)                  | 0               | 2               | 1               |
| Diabetes mellitus                  |                 |                 |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                  | 1               | 0               | 0               |
| Hypercalcaemia                     |                 |                 |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 2 / 11 (18.18%) |
| occurrences (all)                  | 0               | 3               | 3               |
| Hyperglycaemia                     |                 |                 |                 |
| subjects affected / exposed        | 3 / 16 (18.75%) | 0 / 15 (0.00%)  | 1 / 11 (9.09%)  |
| occurrences (all)                  | 9               | 0               | 1               |
| Hyperkalaemia                      |                 |                 |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0               |
| Hypernatraemia                     |                 |                 |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                  | 1               | 0               | 0               |
| Hyperphosphataemia                 |                 |                 |                 |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Hyperuricaemia              |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Hypoalbuminaemia            |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 3               | 1               | 0              |
| Hypocalcaemia               |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 1 / 11 (9.09%) |
| occurrences (all)           | 1               | 0               | 1              |
| Hypoglycaemia               |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 15 (6.67%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 2               | 0              |
| Hypokalaemia                |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 2 / 15 (13.33%) | 1 / 11 (9.09%) |
| occurrences (all)           | 3               | 3               | 1              |
| Hypomagnesaemia             |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Hyponatraemia               |                 |                 |                |
| subjects affected / exposed | 2 / 16 (12.50%) | 3 / 15 (20.00%) | 1 / 11 (9.09%) |
| occurrences (all)           | 4               | 3               | 1              |
| Hypophosphataemia           |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 15 (13.33%) | 1 / 11 (9.09%) |
| occurrences (all)           | 0               | 3               | 2              |

| <b>Non-serious adverse events</b>                                   | All Phase I q2w   | 3 mg/kg q4w     | 5 mg/kg q4w       |
|---|-------------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events               |                   |                 |                   |
| subjects affected / exposed   | 42 / 42 (100.00%) | 6 / 6 (100.00%) | 10 / 10 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                 |                   |
| Cancer pain   |                   |                 |                   |
| subjects affected / exposed   | 0 / 42 (0.00%)    | 0 / 6 (0.00%)   | 0 / 10 (0.00%)    |
| occurrences (all)   | 0                 | 0               | 0                 |
| Tumour haemorrhage  |                   |                 |                   |

|  |                  |                |                 |
|--|------------------|----------------|-----------------|
| subjects affected / exposed                          | 2 / 42 (4.76%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 2                | 0              | 0               |
| Tumour pain  |                  |                |                 |
| subjects affected / exposed                          | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 0                | 0              | 0               |
| Vascular disorders                                   |                  |                |                 |
| Deep vein thrombosis                                 |                  |                |                 |
| subjects affected / exposed                          | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 1                | 0              | 0               |
| Hot flush  |                  |                |                 |
| subjects affected / exposed                          | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 1                | 0              | 0               |
| Hypotension  |                  |                |                 |
| subjects affected / exposed                          | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 1                | 0              | 0               |
| Lymphoedema  |                  |                |                 |
| subjects affected / exposed                          | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 1                | 0              | 0               |
| General disorders and administration site conditions |                  |                |                 |
| Asthenia   |                  |                |                 |
| subjects affected / exposed                          | 2 / 42 (4.76%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 2                | 0              | 0               |
| Chills   |                  |                |                 |
| subjects affected / exposed                          | 4 / 42 (9.52%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 4                | 0              | 0               |
| Face oedema  |                  |                |                 |
| subjects affected / exposed                          | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                                    | 1                | 0              | 1               |
| Fatigue  |                  |                |                 |
| subjects affected / exposed                          | 15 / 42 (35.71%) | 2 / 6 (33.33%) | 5 / 10 (50.00%) |
| occurrences (all)                                    | 16               | 2              | 6               |
| Inflammation   |                  |                |                 |
| subjects affected / exposed                          | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                                    | 1                | 0              | 0               |
| Influenza like illness                               |                  |                |                 |

|  |                 |               |                 |
|--|-----------------|---------------|-----------------|
| subjects affected / exposed              | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 1               | 0             | 0               |
| Malaise                                  |                 |               |                 |
| subjects affected / exposed              | 2 / 42 (4.76%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 2               | 0             | 0               |
| Non-cardiac chest pain                   |                 |               |                 |
| subjects affected / exposed              | 4 / 42 (9.52%)  | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                        | 4               | 0             | 1               |
| Oedema                                   |                 |               |                 |
| subjects affected / exposed              | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 1               | 0             | 0               |
| Oedema peripheral                        |                 |               |                 |
| subjects affected / exposed              | 5 / 42 (11.90%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                        | 6               | 0             | 2               |
| Pain                                     |                 |               |                 |
| subjects affected / exposed              | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 1               | 0             | 0               |
| Peripheral swelling                      |                 |               |                 |
| subjects affected / exposed              | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 1               | 0             | 0               |
| Pyrexia                                  |                 |               |                 |
| subjects affected / exposed              | 5 / 42 (11.90%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                        | 7               | 0             | 1               |
| Swelling face                            |                 |               |                 |
| subjects affected / exposed              | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 1               | 0             | 0               |
| Immune system disorders                  |                 |               |                 |
| Food allergy                             |                 |               |                 |
| subjects affected / exposed              | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                        | 1               | 0             | 0               |
| Seasonal allergy                         |                 |               |                 |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                        | 0               | 0             | 1               |
| Reproductive system and breast disorders |                 |               |                 |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| Pelvic pain                                     |                  |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1                | 0              | 0               |
| Vulvovaginal pain                               |                  |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1                | 0              | 0               |
| Respiratory, thoracic and mediastinal disorders |                  |                |                 |
| Cough   |                  |                |                 |
| subjects affected / exposed                     | 7 / 42 (16.67%)  | 0 / 6 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)                               | 10               | 0              | 3               |
| Dyspnoea  |                  |                |                 |
| subjects affected / exposed                     | 14 / 42 (33.33%) | 0 / 6 (0.00%)  | 4 / 10 (40.00%) |
| occurrences (all)                               | 21               | 0              | 4               |
| Dyspnoea exertional                             |                  |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1                | 0              | 0               |
| Haemoptysis                                     |                  |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1                | 0              | 0               |
| Hiccups   |                  |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%)   | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                               | 0                | 1              | 0               |
| Hypoxia   |                  |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1                | 0              | 0               |
| Oropharyngeal pain                              |                  |                |                 |
| subjects affected / exposed                     | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1                | 0              | 0               |
| Pleural effusion                                |                  |                |                 |
| subjects affected / exposed                     | 5 / 42 (11.90%)  | 0 / 6 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                               | 6                | 0              | 4               |
| Pneumonitis                                     |                  |                |                 |
| subjects affected / exposed                     | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 0                | 0              | 0               |
| Productive cough                                |                  |                |                 |



|                                    |                |                |                 |
|------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed        | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 1              | 0              | 1               |
| Respiratory tract congestion       |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Sinus congestion                   |                |                |                 |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 0              | 0              | 1               |
| Tachypnoea                         |                |                |                 |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 0              | 0              | 1               |
| Upper respiratory tract congestion |                |                |                 |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 0              | 0              | 1               |
| Psychiatric disorders              |                |                |                 |
| Affective disorder                 |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Agitation                          |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Anxiety                            |                |                |                 |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Confusional state                  |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Depression                         |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1              | 1              | 0               |
| Hallucination                      |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Insomnia                           |                |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%) | 1 / 6 (16.67%) | 3 / 10 (30.00%) |
| occurrences (all)                  | 1              | 1              | 3               |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| Investigations                              |                 |               |                 |
| Alanine aminotransferase increased          |                 |               |                 |
| subjects affected / exposed                 | 2 / 42 (4.76%)  | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                           | 3               | 0             | 1               |
| Aspartate aminotransferase increased        |                 |               |                 |
| subjects affected / exposed                 | 5 / 42 (11.90%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                           | 6               | 0             | 1               |
| Bacterial test positive                     |                 |               |                 |
| subjects affected / exposed                 | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                           | 1               | 0             | 0               |
| Blood alkaline phosphatase increased        |                 |               |                 |
| subjects affected / exposed                 | 5 / 42 (11.90%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                           | 7               | 0             | 0               |
| Blood bilirubin increased                   |                 |               |                 |
| subjects affected / exposed                 | 2 / 42 (4.76%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                           | 2               | 0             | 0               |
| Blood creatinine decreased                  |                 |               |                 |
| subjects affected / exposed                 | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                           | 1               | 0             | 0               |
| Blood creatinine increased                  |                 |               |                 |
| subjects affected / exposed                 | 2 / 42 (4.76%)  | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                           | 3               | 0             | 1               |
| Blood thyroid stimulating hormone increased |                 |               |                 |
| subjects affected / exposed                 | 0 / 42 (0.00%)  | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                           | 0               | 0             | 1               |
| Gamma-glutamyltransferase increased         |                 |               |                 |
| subjects affected / exposed                 | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                           | 1               | 0             | 0               |
| Lymphocyte count decreased                  |                 |               |                 |
| subjects affected / exposed                 | 1 / 42 (2.38%)  | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                           | 3               | 0             | 0               |
| Transaminases increased                     |                 |               |                 |
| subjects affected / exposed                 | 2 / 42 (4.76%)  | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                           | 2               | 0             | 1               |
| Weight decreased                            |                 |               |                 |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 7 / 42 (16.67%)<br>7 | 1 / 6 (16.67%)<br>1 | 3 / 10 (30.00%)<br>3 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 42 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 10 (0.00%)<br>0  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>2  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                                       |                      |                     |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 42 (2.38%)<br>1  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 42 (4.76%)<br>2  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Joint dislocation<br>subjects affected / exposed<br>occurrences (all)                | 1 / 42 (2.38%)<br>1  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Ligament rupture<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 42 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Post-traumatic pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 42 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 42 (7.14%)<br>4  | 1 / 6 (16.67%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)               | 0 / 42 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Cardiac disorders  |                      |                     |                      |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 42 (2.38%)<br>1  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Sinus tachycardia  |                      |                     |                      |

|                             |                  |                |                 |
|-----------------------------|------------------|----------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Tachycardia                 |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 1                | 0              | 1               |
| Nervous system disorders    |                  |                |                 |
| Amnesia                     |                  |                |                 |
| subjects affected / exposed | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 0                | 0              | 0               |
| Aphasia                     |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Dizziness                   |                  |                |                 |
| subjects affected / exposed | 10 / 42 (23.81%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 13               | 0              | 0               |
| Dysarthria                  |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Dysgeusia                   |                  |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)   | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 2                | 0              | 1               |
| Headache                    |                  |                |                 |
| subjects affected / exposed | 6 / 42 (14.29%)  | 1 / 6 (16.67%) | 3 / 10 (30.00%) |
| occurrences (all)           | 6                | 2              | 3               |
| Hypoaesthesia               |                  |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)   | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 2                | 1              | 0               |
| Lethargy                    |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Loss of consciousness       |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Neuralgia                   |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |

|  |                  |                |                 |
|--|------------------|----------------|-----------------|
| Neuropathy peripheral                  |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 1              | 0               |
| Paraesthesia                           |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 0              | 0               |
| Paralysis                              |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 0              | 0               |
| Peripheral sensory neuropathy          |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 0              | 0               |
| Presyncope                             |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 0              | 0               |
| Somnolence                             |                  |                |                 |
| subjects affected / exposed            | 0 / 42 (0.00%)   | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                      | 0                | 1              | 0               |
| Taste disorder                         |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 0              | 0               |
| Tremor                                 |                  |                |                 |
| subjects affected / exposed            | 2 / 42 (4.76%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 2                | 0              | 0               |
| Blood and lymphatic system disorders   |                  |                |                 |
| Anaemia                                |                  |                |                 |
| subjects affected / exposed            | 14 / 42 (33.33%) | 1 / 6 (16.67%) | 3 / 10 (30.00%) |
| occurrences (all)                      | 24               | 1              | 3               |
| Disseminated intravascular coagulation |                  |                |                 |
| subjects affected / exposed            | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                      | 1                | 0              | 0               |
| Eosinophilia                           |                  |                |                 |
| subjects affected / exposed            | 0 / 42 (0.00%)   | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                      | 0                | 1              | 0               |
| Iron deficiency anaemia                |                  |                |                 |

|                             |                |               |                 |
|-----------------------------|----------------|---------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Leukocytosis                |                |               |                 |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0             | 1               |
| Leukopenia                  |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Lymph node pain             |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Lymphopenia                 |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Neutropenia                 |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Thrombocytopenia            |                |               |                 |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 3              | 0             | 0               |
| Ear and labyrinth disorders |                |               |                 |
| Hypoacusis                  |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Otorrhoea                   |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Vertigo                     |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Eye disorders               |                |               |                 |
| Periorbital oedema          |                |               |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0               |
| Photopsia                   |                |               |                 |

|                             |                  |                |                 |
|-----------------------------|------------------|----------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Vision blurred              |                  |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2                | 0              | 0               |
| Gastrointestinal disorders  |                  |                |                 |
| Abdominal discomfort        |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Abdominal distension        |                  |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%)   | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 3                | 0              | 2               |
| Abdominal pain              |                  |                |                 |
| subjects affected / exposed | 7 / 42 (16.67%)  | 2 / 6 (33.33%) | 3 / 10 (30.00%) |
| occurrences (all)           | 7                | 5              | 4               |
| Abdominal pain lower        |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Abdominal pain upper        |                  |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 3                | 0              | 0               |
| Ascites                     |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 2 / 6 (33.33%) | 2 / 10 (20.00%) |
| occurrences (all)           | 1                | 2              | 2               |
| Autoimmune colitis          |                  |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1                | 0              | 0               |
| Constipation                |                  |                |                 |
| subjects affected / exposed | 10 / 42 (23.81%) | 2 / 6 (33.33%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 13               | 2              | 0               |
| Diarrhoea                   |                  |                |                 |
| subjects affected / exposed | 14 / 42 (33.33%) | 0 / 6 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)           | 20               | 0              | 5               |
| Dry mouth                   |                  |                |                 |
| subjects affected / exposed | 5 / 42 (11.90%)  | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 5                | 0              | 1               |

|                                  |                  |                |                 |
|----------------------------------|------------------|----------------|-----------------|
| Dyspepsia                        |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 1                | 0              | 1               |
| Dysphagia                        |                  |                |                 |
| subjects affected / exposed      | 3 / 42 (7.14%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 3                | 0              | 0               |
| Flatulence                       |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 1                | 0              | 0               |
| Gastrooesophageal reflux disease |                  |                |                 |
| subjects affected / exposed      | 3 / 42 (7.14%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 3                | 0              | 0               |
| Mouth haemorrhage                |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 1                | 0              | 0               |
| Mouth ulceration                 |                  |                |                 |
| subjects affected / exposed      | 0 / 42 (0.00%)   | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0                | 0              | 1               |
| Nausea                           |                  |                |                 |
| subjects affected / exposed      | 14 / 42 (33.33%) | 3 / 6 (50.00%) | 4 / 10 (40.00%) |
| occurrences (all)                | 16               | 4              | 4               |
| Pancreatic duct dilatation       |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 1                | 0              | 0               |
| Rectal haemorrhage               |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 1                | 0              | 0               |
| Stomatitis                       |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 1                | 0              | 0               |
| Toothache                        |                  |                |                 |
| subjects affected / exposed      | 1 / 42 (2.38%)   | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                | 1                | 0              | 0               |
| Vomiting                         |                  |                |                 |
| subjects affected / exposed      | 10 / 42 (23.81%) | 2 / 6 (33.33%) | 2 / 10 (20.00%) |
| occurrences (all)                | 11               | 4              | 2               |



|  |                |               |                 |
|--|----------------|---------------|-----------------|
| Hepatobiliary disorders                    |                |               |                 |
| Cholecystitis                              |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Hyperbilirubinaemia                        |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Skin and subcutaneous tissue disorders     |                |               |                 |
| Alopecia                                   |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Cold sweat                                 |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Dermatitis acneiform                       |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Dermatitis contact                         |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Erythema                                   |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Hyperhidrosis                              |                |               |                 |
| subjects affected / exposed                | 2 / 42 (4.76%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 2              | 0             | 0               |
| Lichen planus                              |                |               |                 |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 6 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0             | 1               |
| Night sweats                               |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Pain of skin                               |                |               |                 |
| subjects affected / exposed                | 1 / 42 (2.38%) | 0 / 6 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0             | 0               |
| Palmar-plantar erythrodysesthesia syndrome |                |               |                 |

|                             |                 |                |                 |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Papule                      |                 |                |                 |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0               | 0              | 1               |
| Pruritus                    |                 |                |                 |
| subjects affected / exposed | 9 / 42 (21.43%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 10              | 0              | 0               |
| Rash                        |                 |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2               | 0              | 0               |
| Rash erythematous           |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Rash maculo-papular         |                 |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 3               | 0              | 0               |
| Skin ulcer                  |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Vitiligo                    |                 |                |                 |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0               |
| Renal and urinary disorders |                 |                |                 |
| Acute kidney injury         |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Azotaemia                   |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Dysuria                     |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Haematuria                  |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 1              | 0               |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 42 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 42 (2.38%)<br>1  | 0 / 6 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Endocrine disorders  |                      |                     |                      |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)      | 0 / 42 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)       | 7 / 42 (16.67%)<br>7 | 0 / 6 (0.00%)<br>0  | 2 / 10 (20.00%)<br>2 |
| Musculoskeletal and connective tissue disorders                          |                      |                     |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 4 / 42 (9.52%)<br>4  | 1 / 6 (16.67%)<br>1 | 2 / 10 (20.00%)<br>2 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 4 / 42 (9.52%)<br>4  | 1 / 6 (16.67%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)            | 0 / 42 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Coccydynia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 42 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)           | 2 / 42 (4.76%)<br>2  | 0 / 6 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Groin pain   |                      |                     |                      |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Limb discomfort             |                |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Muscle spasms               |                |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Muscular weakness           |                |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 3              | 1              | 0               |
| Musculoskeletal chest pain  |                |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 4              | 0              | 0               |
| Musculoskeletal pain        |                |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 3              | 0              | 1               |
| Myalgia                     |                |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%) | 2 / 6 (33.33%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 3              | 2              | 0               |
| Neck pain                   |                |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Osteoarthritis              |                |                |                 |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 4 / 42 (9.52%) | 1 / 6 (16.67%) | 1 / 10 (10.00%) |
| occurrences (all)           | 4              | 1              | 2               |
| Pathological fracture       |                |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Infections and infestations |                |                |                 |
| Abdominal infection         |                |                |                 |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |

|                               |                |                |                 |
|-------------------------------|----------------|----------------|-----------------|
| Acute sinusitis               |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |
| Bacteraemia                   |                |                |                 |
| subjects affected / exposed   | 2 / 42 (4.76%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 2              | 0              | 0               |
| Fungal skin infection         |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |
| Influenza                     |                |                |                 |
| subjects affected / exposed   | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0               |
| Laryngitis bacterial          |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |
| Nasopharyngitis               |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |
| Oral candidiasis              |                |                |                 |
| subjects affected / exposed   | 2 / 42 (4.76%) | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)             | 2              | 1              | 0               |
| Otitis media                  |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |
| Peritonitis                   |                |                |                 |
| subjects affected / exposed   | 0 / 42 (0.00%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)             | 0              | 0              | 1               |
| Pneumonia                     |                |                |                 |
| subjects affected / exposed   | 3 / 42 (7.14%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 3              | 0              | 0               |
| Postoperative wound infection |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |
| Rhinitis                      |                |                |                 |
| subjects affected / exposed   | 1 / 42 (2.38%) | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0               |

|                                    |                 |                |                 |
|------------------------------------|-----------------|----------------|-----------------|
| Sinusitis                          |                 |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 1               | 0              | 1               |
| Upper respiratory tract infection  |                 |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1               | 0              | 0               |
| Urinary tract infection            |                 |                |                 |
| subjects affected / exposed        | 4 / 42 (9.52%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 6               | 0              | 0               |
| Metabolism and nutrition disorders |                 |                |                 |
| Cachexia                           |                 |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1               | 0              | 0               |
| Decreased appetite                 |                 |                |                 |
| subjects affected / exposed        | 9 / 42 (21.43%) | 2 / 6 (33.33%) | 2 / 10 (20.00%) |
| occurrences (all)                  | 9               | 2              | 2               |
| Dehydration                        |                 |                |                 |
| subjects affected / exposed        | 3 / 42 (7.14%)  | 2 / 6 (33.33%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 3               | 2              | 0               |
| Diabetes mellitus                  |                 |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1               | 0              | 0               |
| Hypercalcaemia                     |                 |                |                 |
| subjects affected / exposed        | 3 / 42 (7.14%)  | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 6               | 1              | 0               |
| Hyperglycaemia                     |                 |                |                 |
| subjects affected / exposed        | 4 / 42 (9.52%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 10              | 0              | 0               |
| Hyperkalaemia                      |                 |                |                 |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 0               | 1              | 0               |
| Hypernatraemia                     |                 |                |                 |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1               | 0              | 0               |
| Hyperphosphataemia                 |                 |                |                 |

|                             |                 |                |                 |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Hyperuricaemia              |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Hypoalbuminaemia            |                 |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 4               | 0              | 0               |
| Hypocalcaemia               |                 |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2               | 0              | 0               |
| Hypoglycaemia               |                 |                |                 |
| subjects affected / exposed | 2 / 42 (4.76%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 3               | 0              | 0               |
| Hypokalaemia                |                 |                |                 |
| subjects affected / exposed | 4 / 42 (9.52%)  | 1 / 6 (16.67%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 7               | 1              | 0               |
| Hypomagnesaemia             |                 |                |                 |
| subjects affected / exposed | 1 / 42 (2.38%)  | 0 / 6 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |
| Hyponatraemia               |                 |                |                 |
| subjects affected / exposed | 6 / 42 (14.29%) | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 8               | 0              | 1               |
| Hypophosphataemia           |                 |                |                 |
| subjects affected / exposed | 3 / 42 (7.14%)  | 0 / 6 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 5               | 0              | 2               |

| <b>Non-serious adverse events</b>                                   | All phase I q4w   | All phase I patients | NSCLC 400mg/q4w  |
|---|-------------------|----------------------|------------------|
| Total subjects affected by non-serious adverse events               |                   |                      |                  |
| subjects affected / exposed   | 16 / 16 (100.00%) | 58 / 58 (100.00%)    | 54 / 59 (91.53%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                      |                  |
| Cancer pain   |                   |                      |                  |
| subjects affected / exposed   | 0 / 16 (0.00%)    | 0 / 58 (0.00%)       | 1 / 59 (1.69%)   |
| occurrences (all)   | 0                 | 0                    | 1                |
| Tumour haemorrhage  |                   |                      |                  |

|   |                      |                        |                        |
|---|----------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 2 / 58 (3.45%)<br>2    | 0 / 59 (0.00%)<br>0    |
| Tumour pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 0 / 58 (0.00%)<br>0    | 0 / 59 (0.00%)<br>0    |
| Vascular disorders<br>Deep vein thrombosis<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 1 / 59 (1.69%)<br>1    |
| Lymphoedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 58 (3.45%)<br>2    | 12 / 59 (20.34%)<br>12 |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 4 / 58 (6.90%)<br>4    | 0 / 59 (0.00%)<br>0    |
| Face oedema<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1  | 2 / 58 (3.45%)<br>2    | 1 / 59 (1.69%)<br>1    |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 7 / 16 (43.75%)<br>8 | 22 / 58 (37.93%)<br>24 | 11 / 59 (18.64%)<br>12 |
| Inflammation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Influenza like illness  |                      |                        |                        |



|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)                        | 0              | 1               | 0               |
| Malaise                                  |                |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%) | 2 / 58 (3.45%)  | 4 / 59 (6.78%)  |
| occurrences (all)                        | 0              | 2               | 4               |
| Non-cardiac chest pain                   |                |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%) | 5 / 58 (8.62%)  | 2 / 59 (3.39%)  |
| occurrences (all)                        | 1              | 5               | 3               |
| Oedema                                   |                |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)                        | 0              | 1               | 0               |
| Oedema peripheral                        |                |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%) | 6 / 58 (10.34%) | 5 / 59 (8.47%)  |
| occurrences (all)                        | 2              | 8               | 5               |
| Pain                                     |                |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 1 / 59 (1.69%)  |
| occurrences (all)                        | 0              | 1               | 1               |
| Peripheral swelling                      |                |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)                        | 0              | 1               | 0               |
| Pyrexia                                  |                |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%) | 6 / 58 (10.34%) | 9 / 59 (15.25%) |
| occurrences (all)                        | 1              | 8               | 13              |
| Swelling face                            |                |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)                        | 0              | 1               | 0               |
| Immune system disorders                  |                |                 |                 |
| Food allergy                             |                |                 |                 |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)                        | 0              | 1               | 0               |
| Seasonal allergy                         |                |                 |                 |
| subjects affected / exposed              | 1 / 16 (6.25%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)                        | 1              | 1               | 0               |
| Reproductive system and breast disorders |                |                 |                 |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| Pelvic pain                                     |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 0               | 1                | 0                |
| Vulvovaginal pain                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 0               | 1                | 0                |
| Respiratory, thoracic and mediastinal disorders |                 |                  |                  |
| Cough   |                 |                  |                  |
| subjects affected / exposed                     | 3 / 16 (18.75%) | 10 / 58 (17.24%) | 13 / 59 (22.03%) |
| occurrences (all)                               | 3               | 13               | 18               |
| Dyspnoea  |                 |                  |                  |
| subjects affected / exposed                     | 4 / 16 (25.00%) | 18 / 58 (31.03%) | 17 / 59 (28.81%) |
| occurrences (all)                               | 4               | 25               | 17               |
| Dyspnoea exertional                             |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 0               | 1                | 0                |
| Haemoptysis                                     |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 2 / 59 (3.39%)   |
| occurrences (all)                               | 0               | 1                | 2                |
| Hiccups   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 1               | 1                | 0                |
| Hypoxia   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 1 / 59 (1.69%)   |
| occurrences (all)                               | 0               | 1                | 1                |
| Oropharyngeal pain                              |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 3 / 59 (5.08%)   |
| occurrences (all)                               | 0               | 1                | 3                |
| Pleural effusion                                |                 |                  |                  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 7 / 58 (12.07%)  | 3 / 59 (5.08%)   |
| occurrences (all)                               | 4               | 10               | 3                |
| Pneumonitis                                     |                 |                  |                  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 58 (0.00%)   | 3 / 59 (5.08%)   |
| occurrences (all)                               | 0               | 0                | 4                |
| Productive cough                                |                 |                  |                  |

|                                    |                 |                |                 |
|------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed        | 1 / 16 (6.25%)  | 2 / 58 (3.45%) | 6 / 59 (10.17%) |
| occurrences (all)                  | 1               | 2              | 6               |
| Respiratory tract congestion       |                 |                |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%) | 0 / 59 (0.00%)  |
| occurrences (all)                  | 0               | 1              | 0               |
| Sinus congestion                   |                 |                |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 1 / 58 (1.72%) | 0 / 59 (0.00%)  |
| occurrences (all)                  | 1               | 1              | 0               |
| Tachypnoea                         |                 |                |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 1 / 58 (1.72%) | 0 / 59 (0.00%)  |
| occurrences (all)                  | 1               | 1              | 0               |
| Upper respiratory tract congestion |                 |                |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 1 / 58 (1.72%) | 0 / 59 (0.00%)  |
| occurrences (all)                  | 1               | 1              | 0               |
| Psychiatric disorders              |                 |                |                 |
| Affective disorder                 |                 |                |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%) | 0 / 59 (0.00%)  |
| occurrences (all)                  | 0               | 1              | 0               |
| Agitation                          |                 |                |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%) | 0 / 59 (0.00%)  |
| occurrences (all)                  | 0               | 1              | 0               |
| Anxiety                            |                 |                |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 0 / 58 (0.00%) | 1 / 59 (1.69%)  |
| occurrences (all)                  | 0               | 0              | 1               |
| Confusional state                  |                 |                |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%) | 1 / 59 (1.69%)  |
| occurrences (all)                  | 0               | 1              | 1               |
| Depression                         |                 |                |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 2 / 58 (3.45%) | 2 / 59 (3.39%)  |
| occurrences (all)                  | 1               | 2              | 2               |
| Hallucination                      |                 |                |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%) | 1 / 59 (1.69%)  |
| occurrences (all)                  | 0               | 1              | 1               |
| Insomnia                           |                 |                |                 |
| subjects affected / exposed        | 4 / 16 (25.00%) | 5 / 58 (8.62%) | 2 / 59 (3.39%)  |
| occurrences (all)                  | 4               | 5              | 2               |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| Investigations                              |                |                 |                |
| Alanine aminotransferase increased          |                |                 |                |
| subjects affected / exposed                 | 1 / 16 (6.25%) | 3 / 58 (5.17%)  | 2 / 59 (3.39%) |
| occurrences (all)                           | 1              | 4               | 2              |
| Aspartate aminotransferase increased        |                |                 |                |
| subjects affected / exposed                 | 1 / 16 (6.25%) | 6 / 58 (10.34%) | 3 / 59 (5.08%) |
| occurrences (all)                           | 1              | 7               | 3              |
| Bacterial test positive                     |                |                 |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0              | 1               | 0              |
| Blood alkaline phosphatase increased        |                |                 |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 5 / 58 (8.62%)  | 2 / 59 (3.39%) |
| occurrences (all)                           | 0              | 7               | 2              |
| Blood bilirubin increased                   |                |                 |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 2 / 58 (3.45%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0              | 2               | 0              |
| Blood creatinine decreased                  |                |                 |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0              | 1               | 0              |
| Blood creatinine increased                  |                |                 |                |
| subjects affected / exposed                 | 1 / 16 (6.25%) | 3 / 58 (5.17%)  | 1 / 59 (1.69%) |
| occurrences (all)                           | 1              | 4               | 1              |
| Blood thyroid stimulating hormone increased |                |                 |                |
| subjects affected / exposed                 | 1 / 16 (6.25%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 1              | 1               | 0              |
| Gamma-glutamyltransferase increased         |                |                 |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 1 / 59 (1.69%) |
| occurrences (all)                           | 0              | 1               | 1              |
| Lymphocyte count decreased                  |                |                 |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0              | 3               | 0              |
| Transaminases increased                     |                |                 |                |
| subjects affected / exposed                 | 1 / 16 (6.25%) | 3 / 58 (5.17%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 1              | 3               | 0              |
| Weight decreased                            |                |                 |                |

|  |                      |                        |                      |
|--|----------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 4 / 16 (25.00%)<br>4 | 11 / 58 (18.97%)<br>11 | 6 / 59 (10.17%)<br>6 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>2    | 0 / 59 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                                       |                      |                        |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 16 (0.00%)<br>0  | 2 / 58 (3.45%)<br>2    | 0 / 59 (0.00%)<br>0  |
| Joint dislocation<br>subjects affected / exposed<br>occurrences (all)                | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| Ligament rupture<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| Post-traumatic pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 16 (6.25%)<br>1  | 4 / 58 (6.90%)<br>5    | 1 / 59 (1.69%)<br>1  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)               | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| Cardiac disorders  |                      |                        |                      |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0  |
| Sinus tachycardia  |                      |                        |                      |

|                             |                 |                  |                |
|-----------------------------|-----------------|------------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 1 / 59 (1.69%) |
| occurrences (all)           | 0               | 1                | 1              |
| Tachycardia                 |                 |                  |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 2 / 58 (3.45%)   | 1 / 59 (1.69%) |
| occurrences (all)           | 1               | 2                | 1              |
| Nervous system disorders    |                 |                  |                |
| Amnesia                     |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 58 (0.00%)   | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 0                | 0              |
| Aphasia                     |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1                | 0              |
| Dizziness                   |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 10 / 58 (17.24%) | 1 / 59 (1.69%) |
| occurrences (all)           | 0               | 13               | 1              |
| Dysarthria                  |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1                | 0              |
| Dysgeusia                   |                 |                  |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 3 / 58 (5.17%)   | 1 / 59 (1.69%) |
| occurrences (all)           | 1               | 3                | 1              |
| Headache                    |                 |                  |                |
| subjects affected / exposed | 4 / 16 (25.00%) | 10 / 58 (17.24%) | 4 / 59 (6.78%) |
| occurrences (all)           | 5               | 11               | 5              |
| Hypoaesthesia               |                 |                  |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 3 / 58 (5.17%)   | 1 / 59 (1.69%) |
| occurrences (all)           | 1               | 3                | 1              |
| Lethargy                    |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1                | 0              |
| Loss of consciousness       |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1                | 0              |
| Neuralgia                   |                 |                  |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1                | 0              |

|   |                      |                        |                        |
|---|----------------------|------------------------|------------------------|
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 16 (6.25%)<br>1  | 2 / 58 (3.45%)<br>2    | 0 / 59 (0.00%)<br>0    |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 1 / 59 (1.69%)<br>1    |
| Paralysis<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 1 / 59 (1.69%)<br>1    |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)             | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 1 / 59 (1.69%)<br>1    |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1    | 1 / 59 (1.69%)<br>1    |
| Taste disorder<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 16 (0.00%)<br>0  | 2 / 58 (3.45%)<br>2    | 0 / 59 (0.00%)<br>0    |
| Blood and lymphatic system disorders  |                      |                        |                        |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                   | 4 / 16 (25.00%)<br>4 | 18 / 58 (31.03%)<br>28 | 16 / 59 (27.12%)<br>18 |
| Disseminated intravascular<br>coagulation<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1    | 0 / 59 (0.00%)<br>0    |
| Iron deficiency anaemia   |                      |                        |                        |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Leukocytosis                |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Leukopenia                  |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Lymph node pain             |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Lymphopenia                 |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 1 / 59 (1.69%) |
| occurrences (all)           | 0              | 1              | 1              |
| Neutropenia                 |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Thrombocytopenia            |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 3              | 0              |
| Ear and labyrinth disorders |                |                |                |
| Hypoacusis                  |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Otorrhoea                   |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Vertigo                     |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Eye disorders               |                |                |                |
| Periorbital oedema          |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Photopsia                   |                |                |                |



|                             |                 |                  |                 |
|-----------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0               |
| Vision blurred              |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 58 (3.45%)   | 0 / 59 (0.00%)  |
| occurrences (all)           | 0               | 2                | 0               |
| Gastrointestinal disorders  |                 |                  |                 |
| Abdominal discomfort        |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0               |
| Abdominal distension        |                 |                  |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 4 / 58 (6.90%)   | 1 / 59 (1.69%)  |
| occurrences (all)           | 2               | 5                | 1               |
| Abdominal pain              |                 |                  |                 |
| subjects affected / exposed | 5 / 16 (31.25%) | 12 / 58 (20.69%) | 3 / 59 (5.08%)  |
| occurrences (all)           | 9               | 16               | 3               |
| Abdominal pain lower        |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0               |
| Abdominal pain upper        |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 3 / 58 (5.17%)   | 1 / 59 (1.69%)  |
| occurrences (all)           | 0               | 3                | 1               |
| Ascites                     |                 |                  |                 |
| subjects affected / exposed | 4 / 16 (25.00%) | 5 / 58 (8.62%)   | 0 / 59 (0.00%)  |
| occurrences (all)           | 4               | 5                | 0               |
| Autoimmune colitis          |                 |                  |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0               |
| Constipation                |                 |                  |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 12 / 58 (20.69%) | 8 / 59 (13.56%) |
| occurrences (all)           | 2               | 15               | 10              |
| Diarrhoea                   |                 |                  |                 |
| subjects affected / exposed | 3 / 16 (18.75%) | 17 / 58 (29.31%) | 8 / 59 (13.56%) |
| occurrences (all)           | 5               | 25               | 17              |
| Dry mouth                   |                 |                  |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 6 / 58 (10.34%)  | 3 / 59 (5.08%)  |
| occurrences (all)           | 1               | 6                | 3               |

|                                  |                 |                  |                 |
|----------------------------------|-----------------|------------------|-----------------|
| Dyspepsia                        |                 |                  |                 |
| subjects affected / exposed      | 1 / 16 (6.25%)  | 2 / 58 (3.45%)   | 2 / 59 (3.39%)  |
| occurrences (all)                | 1               | 2                | 2               |
| Dysphagia                        |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 3 / 58 (5.17%)   | 0 / 59 (0.00%)  |
| occurrences (all)                | 0               | 3                | 0               |
| Flatulence                       |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)                | 0               | 1                | 0               |
| Gastrooesophageal reflux disease |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 3 / 58 (5.17%)   | 1 / 59 (1.69%)  |
| occurrences (all)                | 0               | 3                | 1               |
| Mouth haemorrhage                |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)                | 0               | 1                | 0               |
| Mouth ulceration                 |                 |                  |                 |
| subjects affected / exposed      | 1 / 16 (6.25%)  | 1 / 58 (1.72%)   | 1 / 59 (1.69%)  |
| occurrences (all)                | 1               | 1                | 1               |
| Nausea                           |                 |                  |                 |
| subjects affected / exposed      | 7 / 16 (43.75%) | 21 / 58 (36.21%) | 9 / 59 (15.25%) |
| occurrences (all)                | 8               | 24               | 10              |
| Pancreatic duct dilatation       |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)                | 0               | 1                | 0               |
| Rectal haemorrhage               |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)                | 0               | 1                | 0               |
| Stomatitis                       |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 1 / 59 (1.69%)  |
| occurrences (all)                | 0               | 1                | 1               |
| Toothache                        |                 |                  |                 |
| subjects affected / exposed      | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)  |
| occurrences (all)                | 0               | 1                | 0               |
| Vomiting                         |                 |                  |                 |
| subjects affected / exposed      | 4 / 16 (25.00%) | 14 / 58 (24.14%) | 8 / 59 (13.56%) |
| occurrences (all)                | 6               | 17               | 10              |

|  |  |                |                |
|--|--|----------------|----------------|
| Hepatobiliary disorders                |  |                |                |
|  | Cholecystitis                              |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
| Hyperbilirubinaemia                    |  |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
| Skin and subcutaneous tissue disorders |  |                |                |
|  | Alopecia                                   |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Cold sweat                                 |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Dermatitis acneiform                       |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Dermatitis contact                         |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Erythema                                   |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Hyperhidrosis                              |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 2 / 58 (3.45%) |
|  | occurrences (all)                          | 0              | 2              |
|  |  |                |                |
|  | Lichen planus                              |                |                |
|  | subjects affected / exposed                | 1 / 16 (6.25%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 1              | 1              |
|  |  |                |                |
|  | Night sweats                               |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Pain of skin                               |                |                |
|  | subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 58 (1.72%) |
|  | occurrences (all)                          | 0              | 1              |
|  |  |                |                |
|  | Palmar-plantar erythrodysesthesia syndrome |                |                |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Papule                      |                |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 1              | 1               | 0               |
| Pruritus                    |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 9 / 58 (15.52%) | 7 / 59 (11.86%) |
| occurrences (all)           | 0              | 10              | 7               |
| Rash                        |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 58 (3.45%)  | 5 / 59 (8.47%)  |
| occurrences (all)           | 0              | 2               | 5               |
| Rash erythematous           |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Rash maculo-papular         |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 3 / 58 (5.17%)  | 2 / 59 (3.39%)  |
| occurrences (all)           | 0              | 3               | 2               |
| Skin ulcer                  |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Vitiligo                    |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 58 (0.00%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Renal and urinary disorders |                |                 |                 |
| Acute kidney injury         |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Azotaemia                   |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Dysuria                     |                |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Haematuria                  |                |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%) | 2 / 58 (3.45%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 1              | 2               | 0               |

|  |                      |                      |                       |
|--|----------------------|----------------------|-----------------------|
| Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1  | 0 / 59 (0.00%)<br>0   |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1  | 0 / 59 (0.00%)<br>0   |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 16 (6.25%)<br>1  | 2 / 58 (3.45%)<br>2  | 0 / 59 (0.00%)<br>0   |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1  | 0 / 59 (0.00%)<br>0   |
| Endocrine disorders  |                      |                      |                       |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)      | 0 / 16 (0.00%)<br>0  | 0 / 58 (0.00%)<br>0  | 5 / 59 (8.47%)<br>5   |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)       | 2 / 16 (12.50%)<br>2 | 9 / 58 (15.52%)<br>9 | 4 / 59 (6.78%)<br>4   |
| Musculoskeletal and connective tissue disorders                          |                      |                      |                       |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 3 / 16 (18.75%)<br>3 | 7 / 58 (12.07%)<br>7 | 8 / 59 (13.56%)<br>9  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 1 / 16 (6.25%)<br>1  | 5 / 58 (8.62%)<br>5  | 8 / 59 (13.56%)<br>10 |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)            | 0 / 16 (0.00%)<br>0  | 0 / 58 (0.00%)<br>0  | 3 / 59 (5.08%)<br>5   |
| Coccydynia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 16 (6.25%)<br>1  | 1 / 58 (1.72%)<br>1  | 0 / 59 (0.00%)<br>0   |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 16 (6.25%)<br>1  | 3 / 58 (5.17%)<br>3  | 1 / 59 (1.69%)<br>1   |
| Groin pain   |                      |                      |                       |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 58 (3.45%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 2               | 0              |
| Limb discomfort             |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Muscle spasms               |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 58 (3.45%)  | 2 / 59 (3.39%) |
| occurrences (all)           | 0               | 2               | 2              |
| Muscular weakness           |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 4 / 58 (6.90%)  | 1 / 59 (1.69%) |
| occurrences (all)           | 1               | 4               | 1              |
| Musculoskeletal chest pain  |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 58 (3.45%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 4               | 0              |
| Musculoskeletal pain        |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 4 / 58 (6.90%)  | 5 / 59 (8.47%) |
| occurrences (all)           | 1               | 4               | 7              |
| Myalgia                     |                 |                 |                |
| subjects affected / exposed | 2 / 16 (12.50%) | 5 / 58 (8.62%)  | 4 / 59 (6.78%) |
| occurrences (all)           | 2               | 5               | 5              |
| Neck pain                   |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 58 (3.45%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 2               | 0              |
| Osteoarthritis              |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 1               | 1               | 0              |
| Pain in extremity           |                 |                 |                |
| subjects affected / exposed | 2 / 16 (12.50%) | 6 / 58 (10.34%) | 1 / 59 (1.69%) |
| occurrences (all)           | 3               | 7               | 1              |
| Pathological fracture       |                 |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Infections and infestations |                 |                 |                |
| Abdominal infection         |                 |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 1               | 1               | 0              |

|                               |                |                |                |
|-------------------------------|----------------|----------------|----------------|
| Acute sinusitis               |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Bacteraemia                   |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 2 / 58 (3.45%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 2              | 0              |
| Fungal skin infection         |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Influenza                     |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 0 / 58 (0.00%) | 4 / 59 (6.78%) |
| occurrences (all)             | 0              | 0              | 4              |
| Laryngitis bacterial          |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Nasopharyngitis               |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 2 / 59 (3.39%) |
| occurrences (all)             | 0              | 1              | 3              |
| Oral candidiasis              |                |                |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 3 / 58 (5.17%) | 0 / 59 (0.00%) |
| occurrences (all)             | 1              | 3              | 0              |
| Otitis media                  |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Peritonitis                   |                |                |                |
| subjects affected / exposed   | 1 / 16 (6.25%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 1              | 1              | 0              |
| Pneumonia                     |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 3 / 58 (5.17%) | 3 / 59 (5.08%) |
| occurrences (all)             | 0              | 3              | 4              |
| Postoperative wound infection |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Rhinitis                      |                |                |                |
| subjects affected / exposed   | 0 / 16 (0.00%) | 1 / 58 (1.72%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |

|                                    |                 |                  |                  |
|------------------------------------|-----------------|------------------|------------------|
| Sinusitis                          |                 |                  |                  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 2 / 58 (3.45%)   | 0 / 59 (0.00%)   |
| occurrences (all)                  | 1               | 2                | 0                |
| Upper respiratory tract infection  |                 |                  |                  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 3 / 59 (5.08%)   |
| occurrences (all)                  | 0               | 1                | 3                |
| Urinary tract infection            |                 |                  |                  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 4 / 58 (6.90%)   | 2 / 59 (3.39%)   |
| occurrences (all)                  | 0               | 6                | 2                |
| Metabolism and nutrition disorders |                 |                  |                  |
| Cachexia                           |                 |                  |                  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)   |
| occurrences (all)                  | 0               | 1                | 0                |
| Decreased appetite                 |                 |                  |                  |
| subjects affected / exposed        | 4 / 16 (25.00%) | 13 / 58 (22.41%) | 18 / 59 (30.51%) |
| occurrences (all)                  | 4               | 13               | 19               |
| Dehydration                        |                 |                  |                  |
| subjects affected / exposed        | 2 / 16 (12.50%) | 5 / 58 (8.62%)   | 0 / 59 (0.00%)   |
| occurrences (all)                  | 2               | 5                | 0                |
| Diabetes mellitus                  |                 |                  |                  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 1 / 59 (1.69%)   |
| occurrences (all)                  | 0               | 1                | 1                |
| Hypercalcaemia                     |                 |                  |                  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 4 / 58 (6.90%)   | 4 / 59 (6.78%)   |
| occurrences (all)                  | 1               | 7                | 4                |
| Hyperglycaemia                     |                 |                  |                  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 4 / 58 (6.90%)   | 1 / 59 (1.69%)   |
| occurrences (all)                  | 0               | 10               | 1                |
| Hyperkalaemia                      |                 |                  |                  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 1 / 58 (1.72%)   | 1 / 59 (1.69%)   |
| occurrences (all)                  | 1               | 1                | 1                |
| Hypernatraemia                     |                 |                  |                  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 58 (1.72%)   | 0 / 59 (0.00%)   |
| occurrences (all)                  | 0               | 1                | 0                |
| Hyperphosphataemia                 |                 |                  |                  |



|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hyperuricaemia              |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypoalbuminaemia            |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 58 (3.45%)  | 3 / 59 (5.08%) |
| occurrences (all)           | 0              | 4               | 9              |
| Hypocalcaemia               |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 58 (3.45%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Hypoglycaemia               |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 58 (3.45%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 3               | 0              |
| Hypokalaemia                |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 5 / 58 (8.62%)  | 2 / 59 (3.39%) |
| occurrences (all)           | 1              | 8               | 4              |
| Hypomagnesaemia             |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 58 (1.72%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hyponatraemia               |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 7 / 58 (12.07%) | 2 / 59 (3.39%) |
| occurrences (all)           | 1              | 9               | 2              |
| Hypophosphataemia           |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 4 / 58 (6.90%)  | 3 / 59 (5.08%) |
| occurrences (all)           | 2              | 7               | 15             |

| <b>Non-serious adverse events</b>                                   | Melanoma<br>400mg/q4w | TNBC 400mg/q4w   | NSCLC 300mg/q3w  |
|---|-----------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events               |                       |                  |                  |
| subjects affected / exposed   | 55 / 61 (90.16%)      | 37 / 40 (92.50%) | 56 / 59 (94.92%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                  |                  |
| Cancer pain   |                       |                  |                  |
| subjects affected / exposed   | 2 / 61 (3.28%)        | 0 / 40 (0.00%)   | 5 / 59 (8.47%)   |
| occurrences (all)   | 2                     | 0                | 5                |
| Tumour haemorrhage  |                       |                  |                  |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| subjects affected / exposed                          | 1 / 61 (1.64%)   | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                                    | 1                | 0                | 0                |
| Tumour pain  |                  |                  |                  |
| subjects affected / exposed                          | 1 / 61 (1.64%)   | 6 / 40 (15.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                                    | 1                | 6                | 0                |
| Vascular disorders                                   |                  |                  |                  |
| Deep vein thrombosis                                 |                  |                  |                  |
| subjects affected / exposed                          | 0 / 61 (0.00%)   | 2 / 40 (5.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                                    | 0                | 2                | 0                |
| Hot flush  |                  |                  |                  |
| subjects affected / exposed                          | 0 / 61 (0.00%)   | 1 / 40 (2.50%)   | 2 / 59 (3.39%)   |
| occurrences (all)                                    | 0                | 1                | 2                |
| Hypotension  |                  |                  |                  |
| subjects affected / exposed                          | 0 / 61 (0.00%)   | 0 / 40 (0.00%)   | 1 / 59 (1.69%)   |
| occurrences (all)                                    | 0                | 0                | 1                |
| Lymphoedema  |                  |                  |                  |
| subjects affected / exposed                          | 1 / 61 (1.64%)   | 1 / 40 (2.50%)   | 0 / 59 (0.00%)   |
| occurrences (all)                                    | 1                | 1                | 0                |
| General disorders and administration site conditions |                  |                  |                  |
| Asthenia   |                  |                  |                  |
| subjects affected / exposed                          | 8 / 61 (13.11%)  | 4 / 40 (10.00%)  | 12 / 59 (20.34%) |
| occurrences (all)                                    | 11               | 4                | 17               |
| Chills   |                  |                  |                  |
| subjects affected / exposed                          | 1 / 61 (1.64%)   | 2 / 40 (5.00%)   | 2 / 59 (3.39%)   |
| occurrences (all)                                    | 1                | 2                | 2                |
| Face oedema  |                  |                  |                  |
| subjects affected / exposed                          | 0 / 61 (0.00%)   | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                                    | 0                | 0                | 0                |
| Fatigue  |                  |                  |                  |
| subjects affected / exposed                          | 12 / 61 (19.67%) | 13 / 40 (32.50%) | 12 / 59 (20.34%) |
| occurrences (all)                                    | 12               | 14               | 12               |
| Inflammation   |                  |                  |                  |
| subjects affected / exposed                          | 0 / 61 (0.00%)   | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                                    | 0                | 0                | 0                |
| Influenza like illness                               |                  |                  |                  |

|  |                 |                 |                  |
|--|-----------------|-----------------|------------------|
| subjects affected / exposed              | 1 / 61 (1.64%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                        | 1               | 0               | 0                |
| Malaise                                  |                 |                 |                  |
| subjects affected / exposed              | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                        | 0               | 0               | 0                |
| Non-cardiac chest pain                   |                 |                 |                  |
| subjects affected / exposed              | 3 / 61 (4.92%)  | 2 / 40 (5.00%)  | 8 / 59 (13.56%)  |
| occurrences (all)                        | 3               | 2               | 14               |
| Oedema                                   |                 |                 |                  |
| subjects affected / exposed              | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                        | 0               | 0               | 0                |
| Oedema peripheral                        |                 |                 |                  |
| subjects affected / exposed              | 3 / 61 (4.92%)  | 5 / 40 (12.50%) | 4 / 59 (6.78%)   |
| occurrences (all)                        | 4               | 7               | 4                |
| Pain                                     |                 |                 |                  |
| subjects affected / exposed              | 1 / 61 (1.64%)  | 0 / 40 (0.00%)  | 2 / 59 (3.39%)   |
| occurrences (all)                        | 1               | 0               | 2                |
| Peripheral swelling                      |                 |                 |                  |
| subjects affected / exposed              | 3 / 61 (4.92%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                        | 3               | 0               | 0                |
| Pyrexia                                  |                 |                 |                  |
| subjects affected / exposed              | 9 / 61 (14.75%) | 3 / 40 (7.50%)  | 11 / 59 (18.64%) |
| occurrences (all)                        | 11              | 3               | 26               |
| Swelling face                            |                 |                 |                  |
| subjects affected / exposed              | 1 / 61 (1.64%)  | 0 / 40 (0.00%)  | 1 / 59 (1.69%)   |
| occurrences (all)                        | 1               | 0               | 1                |
| Immune system disorders                  |                 |                 |                  |
| Food allergy                             |                 |                 |                  |
| subjects affected / exposed              | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                        | 0               | 0               | 0                |
| Seasonal allergy                         |                 |                 |                  |
| subjects affected / exposed              | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                        | 0               | 0               | 0                |
| Reproductive system and breast disorders |                 |                 |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| Pelvic pain                                     |                 |                  |                  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 0 / 40 (0.00%)   | 1 / 59 (1.69%)   |
| occurrences (all)                               | 1               | 0                | 1                |
| Vulvovaginal pain                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 0               | 0                | 0                |
| Respiratory, thoracic and mediastinal disorders |                 |                  |                  |
| Cough   |                 |                  |                  |
| subjects affected / exposed                     | 8 / 61 (13.11%) | 10 / 40 (25.00%) | 20 / 59 (33.90%) |
| occurrences (all)                               | 10              | 10               | 22               |
| Dyspnoea  |                 |                  |                  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 10 / 40 (25.00%) | 18 / 59 (30.51%) |
| occurrences (all)                               | 2               | 10               | 18               |
| Dyspnoea exertional                             |                 |                  |                  |
| subjects affected / exposed                     | 0 / 61 (0.00%)  | 2 / 40 (5.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 0               | 2                | 0                |
| Haemoptysis                                     |                 |                  |                  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 0 / 40 (0.00%)   | 2 / 59 (3.39%)   |
| occurrences (all)                               | 1               | 0                | 3                |
| Hiccups   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 1               | 0                | 0                |
| Hypoxia   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 61 (0.00%)  | 1 / 40 (2.50%)   | 1 / 59 (1.69%)   |
| occurrences (all)                               | 0               | 1                | 1                |
| Oropharyngeal pain                              |                 |                  |                  |
| subjects affected / exposed                     | 0 / 61 (0.00%)  | 1 / 40 (2.50%)   | 1 / 59 (1.69%)   |
| occurrences (all)                               | 0               | 1                | 1                |
| Pleural effusion                                |                 |                  |                  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 4 / 40 (10.00%)  | 3 / 59 (5.08%)   |
| occurrences (all)                               | 1               | 4                | 5                |
| Pneumonitis                                     |                 |                  |                  |
| subjects affected / exposed                     | 3 / 61 (4.92%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                               | 4               | 0                | 0                |
| Productive cough                                |                 |                  |                  |

|                                    |                |                 |                |
|------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed        | 1 / 61 (1.64%) | 3 / 40 (7.50%)  | 2 / 59 (3.39%) |
| occurrences (all)                  | 1              | 3               | 4              |
| Respiratory tract congestion       |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Sinus congestion                   |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Tachypnoea                         |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Upper respiratory tract congestion |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Psychiatric disorders              |                |                 |                |
| Affective disorder                 |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Agitation                          |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 1 / 40 (2.50%)  | 1 / 59 (1.69%) |
| occurrences (all)                  | 0              | 1               | 1              |
| Anxiety                            |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 2 / 40 (5.00%)  | 3 / 59 (5.08%) |
| occurrences (all)                  | 0              | 2               | 3              |
| Confusional state                  |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 1 / 40 (2.50%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 1               | 0              |
| Depression                         |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 1 / 40 (2.50%)  | 2 / 59 (3.39%) |
| occurrences (all)                  | 0              | 1               | 2              |
| Hallucination                      |                |                 |                |
| subjects affected / exposed        | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Insomnia                           |                |                 |                |
| subjects affected / exposed        | 6 / 61 (9.84%) | 4 / 40 (10.00%) | 5 / 59 (8.47%) |
| occurrences (all)                  | 6              | 4               | 6              |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Investigations                              |                 |                 |                |
| Alanine aminotransferase increased          |                 |                 |                |
| subjects affected / exposed                 | 7 / 61 (11.48%) | 5 / 40 (12.50%) | 5 / 59 (8.47%) |
| occurrences (all)                           | 7               | 7               | 7              |
| Aspartate aminotransferase increased        |                 |                 |                |
| subjects affected / exposed                 | 7 / 61 (11.48%) | 8 / 40 (20.00%) | 5 / 59 (8.47%) |
| occurrences (all)                           | 7               | 10              | 6              |
| Bacterial test positive                     |                 |                 |                |
| subjects affected / exposed                 | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0               | 0               | 0              |
| Blood alkaline phosphatase increased        |                 |                 |                |
| subjects affected / exposed                 | 2 / 61 (3.28%)  | 6 / 40 (15.00%) | 3 / 59 (5.08%) |
| occurrences (all)                           | 2               | 6               | 3              |
| Blood bilirubin increased                   |                 |                 |                |
| subjects affected / exposed                 | 1 / 61 (1.64%)  | 0 / 40 (0.00%)  | 3 / 59 (5.08%) |
| occurrences (all)                           | 4               | 0               | 4              |
| Blood creatinine decreased                  |                 |                 |                |
| subjects affected / exposed                 | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0               | 0               | 0              |
| Blood creatinine increased                  |                 |                 |                |
| subjects affected / exposed                 | 4 / 61 (6.56%)  | 1 / 40 (2.50%)  | 4 / 59 (6.78%) |
| occurrences (all)                           | 9               | 1               | 8              |
| Blood thyroid stimulating hormone increased |                 |                 |                |
| subjects affected / exposed                 | 0 / 61 (0.00%)  | 1 / 40 (2.50%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0               | 1               | 0              |
| Gamma-glutamyltransferase increased         |                 |                 |                |
| subjects affected / exposed                 | 1 / 61 (1.64%)  | 2 / 40 (5.00%)  | 3 / 59 (5.08%) |
| occurrences (all)                           | 1               | 2               | 3              |
| Lymphocyte count decreased                  |                 |                 |                |
| subjects affected / exposed                 | 3 / 61 (4.92%)  | 2 / 40 (5.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 3               | 2               | 0              |
| Transaminases increased                     |                 |                 |                |
| subjects affected / exposed                 | 0 / 61 (0.00%)  | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)                           | 0               | 0               | 0              |
| Weight decreased                            |                 |                 |                |

|  |                     |                     |                       |
|--|---------------------|---------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 5 / 61 (8.20%)<br>6 | 2 / 40 (5.00%)<br>2 | 9 / 59 (15.25%)<br>10 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 61 (0.00%)<br>0 | 1 / 40 (2.50%)<br>2 | 0 / 59 (0.00%)<br>0   |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 3 / 61 (4.92%)<br>5 | 0 / 40 (0.00%)<br>0 | 1 / 59 (1.69%)<br>2   |
| Injury, poisoning and procedural complications                                       |                     |                     |                       |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 61 (1.64%)<br>1 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 61 (1.64%)<br>1 | 1 / 40 (2.50%)<br>1 | 0 / 59 (0.00%)<br>0   |
| Joint dislocation<br>subjects affected / exposed<br>occurrences (all)                | 0 / 61 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Ligament rupture<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 61 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Post-traumatic pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 61 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 61 (1.64%)<br>1 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)               | 0 / 61 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Cardiac disorders  |                     |                     |                       |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 61 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0   |
| Sinus tachycardia  |                     |                     |                       |

|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 40 (2.50%)  | 2 / 59 (3.39%)   |
| occurrences (all)           | 1              | 1               | 2                |
| Tachycardia                 |                |                 |                  |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 40 (0.00%)  | 1 / 59 (1.69%)   |
| occurrences (all)           | 2              | 0               | 1                |
| Nervous system disorders    |                |                 |                  |
| Amnesia                     |                |                 |                  |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 3 / 59 (5.08%)   |
| occurrences (all)           | 0              | 0               | 3                |
| Aphasia                     |                |                 |                  |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0                |
| Dizziness                   |                |                 |                  |
| subjects affected / exposed | 5 / 61 (8.20%) | 4 / 40 (10.00%) | 10 / 59 (16.95%) |
| occurrences (all)           | 5              | 4               | 10               |
| Dysarthria                  |                |                 |                  |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)           | 1              | 0               | 0                |
| Dysgeusia                   |                |                 |                  |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 1 / 59 (1.69%)   |
| occurrences (all)           | 0              | 0               | 1                |
| Headache                    |                |                 |                  |
| subjects affected / exposed | 4 / 61 (6.56%) | 2 / 40 (5.00%)  | 7 / 59 (11.86%)  |
| occurrences (all)           | 4              | 2               | 8                |
| Hypoaesthesia               |                |                 |                  |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 40 (2.50%)  | 0 / 59 (0.00%)   |
| occurrences (all)           | 1              | 1               | 0                |
| Lethargy                    |                |                 |                  |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0                |
| Loss of consciousness       |                |                 |                  |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0                |
| Neuralgia                   |                |                 |                  |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 40 (2.50%)  | 0 / 59 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |



|   |                        |                      |                       |
|---|------------------------|----------------------|-----------------------|
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 61 (0.00%)<br>0    | 1 / 40 (2.50%)<br>1  | 0 / 59 (0.00%)<br>0   |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 4 / 59 (6.78%)<br>4   |
| Paralysis<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0   |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)             | 1 / 61 (1.64%)<br>1    | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0   |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 1 / 59 (1.69%)<br>1   |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 1 / 59 (1.69%)<br>2   |
| Taste disorder<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 61 (0.00%)<br>0    | 1 / 40 (2.50%)<br>1  | 0 / 59 (0.00%)<br>0   |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0   |
| Blood and lymphatic system disorders  |                        |                      |                       |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                   | 13 / 61 (21.31%)<br>17 | 6 / 40 (15.00%)<br>7 | 8 / 59 (13.56%)<br>10 |
| Disseminated intravascular<br>coagulation<br>subjects affected / exposed<br>occurrences (all) | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0   |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 61 (0.00%)<br>0    | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0   |
| Iron deficiency anaemia   |                        |                      |                       |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Leukocytosis                |                |                |                |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Leukopenia                  |                |                |                |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Lymph node pain             |                |                |                |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Lymphopenia                 |                |                |                |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 40 (2.50%) | 1 / 59 (1.69%) |
| occurrences (all)           | 3              | 1              | 1              |
| Neutropenia                 |                |                |                |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences (all)           | 0              | 0              | 1              |
| Thrombocytopenia            |                |                |                |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 40 (2.50%) | 2 / 59 (3.39%) |
| occurrences (all)           | 3              | 1              | 3              |
| Ear and labyrinth disorders |                |                |                |
| Hypoacusis                  |                |                |                |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Otorrhoea                   |                |                |                |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Vertigo                     |                |                |                |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences (all)           | 1              | 0              | 1              |
| Eye disorders               |                |                |                |
| Periorbital oedema          |                |                |                |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Photopsia                   |                |                |                |

|  |                       |                      |                        |
|--|-----------------------|----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                         | 0 / 61 (0.00%)<br>0   | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0    |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)       | 0 / 61 (0.00%)<br>0   | 1 / 40 (2.50%)<br>2  | 0 / 59 (0.00%)<br>0    |
| Gastrointestinal disorders   |                       |                      |                        |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 0 / 61 (0.00%)<br>0   | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0    |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 1 / 61 (1.64%)<br>1   | 1 / 40 (2.50%)<br>1  | 0 / 59 (0.00%)<br>0    |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 2 / 61 (3.28%)<br>2   | 5 / 40 (12.50%)<br>5 | 5 / 59 (8.47%)<br>5    |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all) | 1 / 61 (1.64%)<br>1   | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0    |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 1 / 61 (1.64%)<br>1   | 0 / 40 (0.00%)<br>0  | 2 / 59 (3.39%)<br>2    |
| Ascites<br>subjects affected / exposed<br>occurrences (all)              | 0 / 61 (0.00%)<br>0   | 2 / 40 (5.00%)<br>2  | 0 / 59 (0.00%)<br>0    |
| Autoimmune colitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 61 (0.00%)<br>0   | 0 / 40 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0    |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 7 / 61 (11.48%)<br>7  | 9 / 40 (22.50%)<br>9 | 9 / 59 (15.25%)<br>9   |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 8 / 61 (13.11%)<br>11 | 1 / 40 (2.50%)<br>1  | 12 / 59 (20.34%)<br>27 |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)            | 3 / 61 (4.92%)<br>3   | 1 / 40 (2.50%)<br>1  | 0 / 59 (0.00%)<br>0    |

|                                  |                 |                  |                  |
|----------------------------------|-----------------|------------------|------------------|
| Dyspepsia                        |                 |                  |                  |
| subjects affected / exposed      | 3 / 61 (4.92%)  | 0 / 40 (0.00%)   | 1 / 59 (1.69%)   |
| occurrences (all)                | 3               | 0                | 1                |
| Dysphagia                        |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 3 / 59 (5.08%)   |
| occurrences (all)                | 0               | 0                | 3                |
| Flatulence                       |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                | 0               | 0                | 0                |
| Gastrooesophageal reflux disease |                 |                  |                  |
| subjects affected / exposed      | 1 / 61 (1.64%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                | 1               | 0                | 0                |
| Mouth haemorrhage                |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                | 0               | 0                | 0                |
| Mouth ulceration                 |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                | 0               | 0                | 0                |
| Nausea                           |                 |                  |                  |
| subjects affected / exposed      | 6 / 61 (9.84%)  | 13 / 40 (32.50%) | 15 / 59 (25.42%) |
| occurrences (all)                | 6               | 14               | 17               |
| Pancreatic duct dilatation       |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                | 0               | 0                | 0                |
| Rectal haemorrhage               |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 0 / 59 (0.00%)   |
| occurrences (all)                | 0               | 0                | 0                |
| Stomatitis                       |                 |                  |                  |
| subjects affected / exposed      | 1 / 61 (1.64%)  | 2 / 40 (5.00%)   | 1 / 59 (1.69%)   |
| occurrences (all)                | 2               | 2                | 1                |
| Toothache                        |                 |                  |                  |
| subjects affected / exposed      | 0 / 61 (0.00%)  | 0 / 40 (0.00%)   | 1 / 59 (1.69%)   |
| occurrences (all)                | 0               | 0                | 1                |
| Vomiting                         |                 |                  |                  |
| subjects affected / exposed      | 8 / 61 (13.11%) | 5 / 40 (12.50%)  | 8 / 59 (13.56%)  |
| occurrences (all)                | 9               | 5                | 14               |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Hepatobiliary disorders                    |                |                |                |
| Cholecystitis                              |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Hyperbilirubinaemia                        |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Skin and subcutaneous tissue disorders     |                |                |                |
| Alopecia                                   |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Cold sweat                                 |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Dermatitis acneiform                       |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Dermatitis contact                         |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Erythema                                   |                |                |                |
| subjects affected / exposed                | 2 / 61 (3.28%) | 1 / 40 (2.50%) | 1 / 59 (1.69%) |
| occurrences (all)                          | 2              | 1              | 1              |
| Hyperhidrosis                              |                |                |                |
| subjects affected / exposed                | 1 / 61 (1.64%) | 1 / 40 (2.50%) | 1 / 59 (1.69%) |
| occurrences (all)                          | 1              | 1              | 1              |
| Lichen planus                              |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Night sweats                               |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 1 / 40 (2.50%) | 1 / 59 (1.69%) |
| occurrences (all)                          | 0              | 1              | 1              |
| Pain of skin                               |                |                |                |
| subjects affected / exposed                | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Palmar-plantar erythrodysesthesia syndrome |                |                |                |

|                             |                  |                 |                |
|-----------------------------|------------------|-----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0                | 0               | 0              |
| Papule                      |                  |                 |                |
| subjects affected / exposed | 0 / 61 (0.00%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0                | 0               | 0              |
| Pruritus                    |                  |                 |                |
| subjects affected / exposed | 8 / 61 (13.11%)  | 4 / 40 (10.00%) | 3 / 59 (5.08%) |
| occurrences (all)           | 10               | 4               | 4              |
| Rash                        |                  |                 |                |
| subjects affected / exposed | 6 / 61 (9.84%)   | 3 / 40 (7.50%)  | 3 / 59 (5.08%) |
| occurrences (all)           | 7                | 3               | 5              |
| Rash erythematous           |                  |                 |                |
| subjects affected / exposed | 1 / 61 (1.64%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 1                | 0               | 0              |
| Rash maculo-papular         |                  |                 |                |
| subjects affected / exposed | 3 / 61 (4.92%)   | 0 / 40 (0.00%)  | 1 / 59 (1.69%) |
| occurrences (all)           | 5                | 0               | 2              |
| Skin ulcer                  |                  |                 |                |
| subjects affected / exposed | 1 / 61 (1.64%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 1                | 0               | 0              |
| Vitiligo                    |                  |                 |                |
| subjects affected / exposed | 10 / 61 (16.39%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 10               | 0               | 0              |
| Renal and urinary disorders |                  |                 |                |
| Acute kidney injury         |                  |                 |                |
| subjects affected / exposed | 1 / 61 (1.64%)   | 0 / 40 (0.00%)  | 1 / 59 (1.69%) |
| occurrences (all)           | 1                | 0               | 1              |
| Azotaemia                   |                  |                 |                |
| subjects affected / exposed | 0 / 61 (0.00%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 0                | 0               | 0              |
| Dysuria                     |                  |                 |                |
| subjects affected / exposed | 1 / 61 (1.64%)   | 1 / 40 (2.50%)  | 2 / 59 (3.39%) |
| occurrences (all)           | 1                | 1               | 5              |
| Haematuria                  |                  |                 |                |
| subjects affected / exposed | 1 / 61 (1.64%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%) |
| occurrences (all)           | 1                | 0               | 0              |

|  |                      |                     |                        |
|--|----------------------|---------------------|------------------------|
| Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 61 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0    |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)  | 0 / 61 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0    |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 61 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0 | 1 / 59 (1.69%)<br>1    |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 0 / 61 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0 | 1 / 59 (1.69%)<br>1    |
| Endocrine disorders  |                      |                     |                        |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)      | 4 / 61 (6.56%)<br>4  | 1 / 40 (2.50%)<br>1 | 2 / 59 (3.39%)<br>2    |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)       | 5 / 61 (8.20%)<br>6  | 3 / 40 (7.50%)<br>3 | 3 / 59 (5.08%)<br>3    |
| Musculoskeletal and connective tissue disorders                          |                      |                     |                        |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 7 / 61 (11.48%)<br>8 | 0 / 40 (0.00%)<br>0 | 6 / 59 (10.17%)<br>6   |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 1 / 61 (1.64%)<br>1  | 3 / 40 (7.50%)<br>4 | 10 / 59 (16.95%)<br>11 |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)            | 2 / 61 (3.28%)<br>2  | 0 / 40 (0.00%)<br>0 | 3 / 59 (5.08%)<br>3    |
| Coccydynia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 61 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0    |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)           | 2 / 61 (3.28%)<br>2  | 1 / 40 (2.50%)<br>1 | 0 / 59 (0.00%)<br>0    |
| Groin pain   |                      |                     |                        |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 40 (0.00%) | 0 / 59 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Limb discomfort             |                |                |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Muscle spasms               |                |                |                 |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 1 / 59 (1.69%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Muscular weakness           |                |                |                 |
| subjects affected / exposed | 4 / 61 (6.56%) | 3 / 40 (7.50%) | 1 / 59 (1.69%)  |
| occurrences (all)           | 4              | 3              | 1               |
| Musculoskeletal chest pain  |                |                |                 |
| subjects affected / exposed | 2 / 61 (3.28%) | 2 / 40 (5.00%) | 2 / 59 (3.39%)  |
| occurrences (all)           | 2              | 2              | 2               |
| Musculoskeletal pain        |                |                |                 |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 40 (2.50%) | 9 / 59 (15.25%) |
| occurrences (all)           | 1              | 1              | 13              |
| Myalgia                     |                |                |                 |
| subjects affected / exposed | 4 / 61 (6.56%) | 1 / 40 (2.50%) | 1 / 59 (1.69%)  |
| occurrences (all)           | 5              | 1              | 1               |
| Neck pain                   |                |                |                 |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 40 (2.50%) | 3 / 59 (5.08%)  |
| occurrences (all)           | 2              | 1              | 3               |
| Osteoarthritis              |                |                |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 4 / 61 (6.56%) | 3 / 40 (7.50%) | 4 / 59 (6.78%)  |
| occurrences (all)           | 4              | 3              | 5               |
| Pathological fracture       |                |                |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Infections and infestations |                |                |                 |
| Abdominal infection         |                |                |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |



|                               |                |                |                |
|-------------------------------|----------------|----------------|----------------|
| Acute sinusitis               |                |                |                |
| subjects affected / exposed   | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 2              | 0              | 0              |
| Bacteraemia                   |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Fungal skin infection         |                |                |                |
| subjects affected / exposed   | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Influenza                     |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences (all)             | 0              | 0              | 1              |
| Laryngitis bacterial          |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Nasopharyngitis               |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 2 / 59 (3.39%) |
| occurrences (all)             | 0              | 0              | 2              |
| Oral candidiasis              |                |                |                |
| subjects affected / exposed   | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 1 / 59 (1.69%) |
| occurrences (all)             | 2              | 0              | 1              |
| Otitis media                  |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Peritonitis                   |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Pneumonia                     |                |                |                |
| subjects affected / exposed   | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 3 / 59 (5.08%) |
| occurrences (all)             | 1              | 0              | 4              |
| Postoperative wound infection |                |                |                |
| subjects affected / exposed   | 1 / 61 (1.64%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Rhinitis                      |                |                |                |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 40 (0.00%) | 0 / 59 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |

|                                    |                  |                 |                  |
|------------------------------------|------------------|-----------------|------------------|
| Sinusitis                          |                  |                 |                  |
| subjects affected / exposed        | 0 / 61 (0.00%)   | 1 / 40 (2.50%)  | 0 / 59 (0.00%)   |
| occurrences (all)                  | 0                | 1               | 0                |
| Upper respiratory tract infection  |                  |                 |                  |
| subjects affected / exposed        | 8 / 61 (13.11%)  | 0 / 40 (0.00%)  | 2 / 59 (3.39%)   |
| occurrences (all)                  | 9                | 0               | 2                |
| Urinary tract infection            |                  |                 |                  |
| subjects affected / exposed        | 2 / 61 (3.28%)   | 1 / 40 (2.50%)  | 2 / 59 (3.39%)   |
| occurrences (all)                  | 2                | 2               | 4                |
| Metabolism and nutrition disorders |                  |                 |                  |
| Cachexia                           |                  |                 |                  |
| subjects affected / exposed        | 1 / 61 (1.64%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                  | 1                | 0               | 0                |
| Decreased appetite                 |                  |                 |                  |
| subjects affected / exposed        | 13 / 61 (21.31%) | 7 / 40 (17.50%) | 17 / 59 (28.81%) |
| occurrences (all)                  | 13               | 7               | 23               |
| Dehydration                        |                  |                 |                  |
| subjects affected / exposed        | 0 / 61 (0.00%)   | 0 / 40 (0.00%)  | 1 / 59 (1.69%)   |
| occurrences (all)                  | 0                | 0               | 1                |
| Diabetes mellitus                  |                  |                 |                  |
| subjects affected / exposed        | 1 / 61 (1.64%)   | 0 / 40 (0.00%)  | 1 / 59 (1.69%)   |
| occurrences (all)                  | 1                | 0               | 2                |
| Hypercalcaemia                     |                  |                 |                  |
| subjects affected / exposed        | 0 / 61 (0.00%)   | 0 / 40 (0.00%)  | 2 / 59 (3.39%)   |
| occurrences (all)                  | 0                | 0               | 3                |
| Hyperglycaemia                     |                  |                 |                  |
| subjects affected / exposed        | 4 / 61 (6.56%)   | 1 / 40 (2.50%)  | 3 / 59 (5.08%)   |
| occurrences (all)                  | 6                | 2               | 4                |
| Hyperkalaemia                      |                  |                 |                  |
| subjects affected / exposed        | 0 / 61 (0.00%)   | 1 / 40 (2.50%)  | 1 / 59 (1.69%)   |
| occurrences (all)                  | 0                | 1               | 2                |
| Hypernatraemia                     |                  |                 |                  |
| subjects affected / exposed        | 0 / 61 (0.00%)   | 0 / 40 (0.00%)  | 0 / 59 (0.00%)   |
| occurrences (all)                  | 0                | 0               | 0                |
| Hyperphosphataemia                 |                  |                 |                  |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 40 (2.50%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Hyperuricaemia              |                |                 |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Hypoalbuminaemia            |                |                 |                 |
| subjects affected / exposed | 2 / 61 (3.28%) | 3 / 40 (7.50%)  | 4 / 59 (6.78%)  |
| occurrences (all)           | 3              | 3               | 9               |
| Hypocalcaemia               |                |                 |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 40 (2.50%)  | 2 / 59 (3.39%)  |
| occurrences (all)           | 0              | 1               | 3               |
| Hypoglycaemia               |                |                 |                 |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 40 (0.00%)  | 0 / 59 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Hypokalaemia                |                |                 |                 |
| subjects affected / exposed | 3 / 61 (4.92%) | 2 / 40 (5.00%)  | 6 / 59 (10.17%) |
| occurrences (all)           | 3              | 3               | 6               |
| Hypomagnesaemia             |                |                 |                 |
| subjects affected / exposed | 2 / 61 (3.28%) | 2 / 40 (5.00%)  | 3 / 59 (5.08%)  |
| occurrences (all)           | 2              | 3               | 5               |
| Hyponatraemia               |                |                 |                 |
| subjects affected / exposed | 3 / 61 (4.92%) | 4 / 40 (10.00%) | 2 / 59 (3.39%)  |
| occurrences (all)           | 3              | 4               | 2               |
| Hypophosphataemia           |                |                 |                 |
| subjects affected / exposed | 4 / 61 (6.56%) | 1 / 40 (2.50%)  | 1 / 59 (1.69%)  |
| occurrences (all)           | 7              | 1               | 2               |

| <b>Non-serious adverse events</b>                                   | ATC 400 mg/q4w   | All phase II patients |  |
|---|------------------|-----------------------|--|
| Total subjects affected by non-serious adverse events               |                  |                       |  |
| subjects affected / exposed   | 39 / 42 (92.86%) | 241 / 261 (92.34%)    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                       |  |
| Cancer pain   |                  |                       |  |
| subjects affected / exposed   | 0 / 42 (0.00%)   | 8 / 261 (3.07%)       |  |
| occurrences (all)   | 0                | 8                     |  |
| Tumour haemorrhage  |                  |                       |  |

|  |                 |                   |  |
|--|-----------------|-------------------|--|
| subjects affected / exposed                          | 1 / 42 (2.38%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                                    | 1               | 2                 |  |
| Tumour pain  |                 |                   |  |
| subjects affected / exposed                          | 3 / 42 (7.14%)  | 10 / 261 (3.83%)  |  |
| occurrences (all)                                    | 4               | 11                |  |
| Vascular disorders                                   |                 |                   |  |
| Deep vein thrombosis                                 |                 |                   |  |
| subjects affected / exposed                          | 0 / 42 (0.00%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                                    | 0               | 2                 |  |
| Hot flush  |                 |                   |  |
| subjects affected / exposed                          | 0 / 42 (0.00%)  | 3 / 261 (1.15%)   |  |
| occurrences (all)                                    | 0               | 3                 |  |
| Hypotension  |                 |                   |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)  | 3 / 261 (1.15%)   |  |
| occurrences (all)                                    | 1               | 3                 |  |
| Lymphoedema  |                 |                   |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)  | 3 / 261 (1.15%)   |  |
| occurrences (all)                                    | 1               | 3                 |  |
| General disorders and administration site conditions |                 |                   |  |
| Asthenia   |                 |                   |  |
| subjects affected / exposed                          | 8 / 42 (19.05%) | 44 / 261 (16.86%) |  |
| occurrences (all)                                    | 8               | 52                |  |
| Chills   |                 |                   |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)  | 6 / 261 (2.30%)   |  |
| occurrences (all)                                    | 1               | 6                 |  |
| Face oedema  |                 |                   |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                                    | 1               | 2                 |  |
| Fatigue  |                 |                   |  |
| subjects affected / exposed                          | 6 / 42 (14.29%) | 54 / 261 (20.69%) |  |
| occurrences (all)                                    | 7               | 57                |  |
| Inflammation   |                 |                   |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)                                    | 1               | 1                 |  |
| Influenza like illness                               |                 |                   |  |

|  |                 |                   |  |
|--|-----------------|-------------------|--|
| subjects affected / exposed              | 1 / 42 (2.38%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                        | 1               | 2                 |  |
| Malaise                                  |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 4 / 261 (1.53%)   |  |
| occurrences (all)                        | 0               | 4                 |  |
| Non-cardiac chest pain                   |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 15 / 261 (5.75%)  |  |
| occurrences (all)                        | 0               | 22                |  |
| Oedema                                   |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)                        | 0               | 0                 |  |
| Oedema peripheral                        |                 |                   |  |
| subjects affected / exposed              | 7 / 42 (16.67%) | 24 / 261 (9.20%)  |  |
| occurrences (all)                        | 8               | 28                |  |
| Pain                                     |                 |                   |  |
| subjects affected / exposed              | 1 / 42 (2.38%)  | 5 / 261 (1.92%)   |  |
| occurrences (all)                        | 1               | 5                 |  |
| Peripheral swelling                      |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 3 / 261 (1.15%)   |  |
| occurrences (all)                        | 0               | 3                 |  |
| Pyrexia                                  |                 |                   |  |
| subjects affected / exposed              | 9 / 42 (21.43%) | 41 / 261 (15.71%) |  |
| occurrences (all)                        | 13              | 66                |  |
| Swelling face                            |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                        | 0               | 2                 |  |
| Immune system disorders                  |                 |                   |  |
| Food allergy                             |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)                        | 0               | 0                 |  |
| Seasonal allergy                         |                 |                   |  |
| subjects affected / exposed              | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)                        | 0               | 0                 |  |
| Reproductive system and breast disorders |                 |                   |  |

|   |                 |                   |  |
|---|-----------------|-------------------|--|
| Pelvic pain                                     |                 |                   |  |
| subjects affected / exposed                     | 0 / 42 (0.00%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                               | 0               | 2                 |  |
| Vulvovaginal pain                               |                 |                   |  |
| subjects affected / exposed                     | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)                               | 0               | 0                 |  |
| Respiratory, thoracic and mediastinal disorders |                 |                   |  |
| Cough   |                 |                   |  |
| subjects affected / exposed                     | 6 / 42 (14.29%) | 57 / 261 (21.84%) |  |
| occurrences (all)                               | 6               | 66                |  |
| Dyspnoea  |                 |                   |  |
| subjects affected / exposed                     | 9 / 42 (21.43%) | 55 / 261 (21.07%) |  |
| occurrences (all)                               | 10              | 57                |  |
| Dyspnoea exertional                             |                 |                   |  |
| subjects affected / exposed                     | 0 / 42 (0.00%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                               | 0               | 2                 |  |
| Haemoptysis                                     |                 |                   |  |
| subjects affected / exposed                     | 4 / 42 (9.52%)  | 9 / 261 (3.45%)   |  |
| occurrences (all)                               | 6               | 12                |  |
| Hiccups   |                 |                   |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                               | 1               | 2                 |  |
| Hypoxia   |                 |                   |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  | 4 / 261 (1.53%)   |  |
| occurrences (all)                               | 1               | 4                 |  |
| Oropharyngeal pain                              |                 |                   |  |
| subjects affected / exposed                     | 4 / 42 (9.52%)  | 9 / 261 (3.45%)   |  |
| occurrences (all)                               | 4               | 9                 |  |
| Pleural effusion                                |                 |                   |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  | 12 / 261 (4.60%)  |  |
| occurrences (all)                               | 1               | 14                |  |
| Pneumonitis                                     |                 |                   |  |
| subjects affected / exposed                     | 0 / 42 (0.00%)  | 6 / 261 (2.30%)   |  |
| occurrences (all)                               | 0               | 8                 |  |
| Productive cough                                |                 |                   |  |

|                                    |                |                  |  |
|------------------------------------|----------------|------------------|--|
| subjects affected / exposed        | 3 / 42 (7.14%) | 15 / 261 (5.75%) |  |
| occurrences (all)                  | 3              | 17               |  |
| Respiratory tract congestion       |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                  | 0              | 0                |  |
| Sinus congestion                   |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                  | 0              | 0                |  |
| Tachypnoea                         |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                  | 0              | 0                |  |
| Upper respiratory tract congestion |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                  | 0              | 0                |  |
| Psychiatric disorders              |                |                  |  |
| Affective disorder                 |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                  | 0              | 0                |  |
| Agitation                          |                |                  |  |
| subjects affected / exposed        | 2 / 42 (4.76%) | 4 / 261 (1.53%)  |  |
| occurrences (all)                  | 2              | 4                |  |
| Anxiety                            |                |                  |  |
| subjects affected / exposed        | 2 / 42 (4.76%) | 8 / 261 (3.07%)  |  |
| occurrences (all)                  | 2              | 8                |  |
| Confusional state                  |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences (all)                  | 0              | 2                |  |
| Depression                         |                |                  |  |
| subjects affected / exposed        | 2 / 42 (4.76%) | 7 / 261 (2.68%)  |  |
| occurrences (all)                  | 2              | 7                |  |
| Hallucination                      |                |                  |  |
| subjects affected / exposed        | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |  |
| occurrences (all)                  | 0              | 1                |  |
| Insomnia                           |                |                  |  |
| subjects affected / exposed        | 2 / 42 (4.76%) | 19 / 261 (7.28%) |  |
| occurrences (all)                  | 2              | 20               |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| Investigations                              |                |                  |  |
| Alanine aminotransferase increased          |                |                  |  |
| subjects affected / exposed                 | 3 / 42 (7.14%) | 22 / 261 (8.43%) |  |
| occurrences (all)                           | 4              | 27               |  |
| Aspartate aminotransferase increased        |                |                  |  |
| subjects affected / exposed                 | 2 / 42 (4.76%) | 25 / 261 (9.58%) |  |
| occurrences (all)                           | 2              | 28               |  |
| Bacterial test positive                     |                |                  |  |
| subjects affected / exposed                 | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                           | 0              | 0                |  |
| Blood alkaline phosphatase increased        |                |                  |  |
| subjects affected / exposed                 | 1 / 42 (2.38%) | 14 / 261 (5.36%) |  |
| occurrences (all)                           | 1              | 14               |  |
| Blood bilirubin increased                   |                |                  |  |
| subjects affected / exposed                 | 1 / 42 (2.38%) | 5 / 261 (1.92%)  |  |
| occurrences (all)                           | 1              | 9                |  |
| Blood creatinine decreased                  |                |                  |  |
| subjects affected / exposed                 | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                           | 0              | 0                |  |
| Blood creatinine increased                  |                |                  |  |
| subjects affected / exposed                 | 0 / 42 (0.00%) | 10 / 261 (3.83%) |  |
| occurrences (all)                           | 0              | 19               |  |
| Blood thyroid stimulating hormone increased |                |                  |  |
| subjects affected / exposed                 | 1 / 42 (2.38%) | 2 / 261 (0.77%)  |  |
| occurrences (all)                           | 1              | 2                |  |
| Gamma-glutamyltransferase increased         |                |                  |  |
| subjects affected / exposed                 | 1 / 42 (2.38%) | 8 / 261 (3.07%)  |  |
| occurrences (all)                           | 1              | 8                |  |
| Lymphocyte count decreased                  |                |                  |  |
| subjects affected / exposed                 | 0 / 42 (0.00%) | 5 / 261 (1.92%)  |  |
| occurrences (all)                           | 0              | 5                |  |
| Transaminases increased                     |                |                  |  |
| subjects affected / exposed                 | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                           | 0              | 0                |  |
| Weight decreased                            |                |                  |  |



|  |                |                  |  |
|--|----------------|------------------|--|
| subjects affected / exposed                    | 2 / 42 (4.76%) | 24 / 261 (9.20%) |  |
| occurrences (all)                              | 2              | 26               |  |
| Weight increased                               |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |  |
| occurrences (all)                              | 0              | 2                |  |
| White blood cell count decreased               |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 4 / 261 (1.53%)  |  |
| occurrences (all)                              | 0              | 7                |  |
| Injury, poisoning and procedural complications |                |                  |  |
| Contusion                                      |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |  |
| occurrences (all)                              | 0              | 1                |  |
| Fall   |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences (all)                              | 0              | 2                |  |
| Joint dislocation                              |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                              | 0              | 0                |  |
| Ligament rupture                               |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                              | 0              | 0                |  |
| Post-traumatic pain                            |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                              | 0              | 0                |  |
| Procedural pain                                |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences (all)                              | 0              | 2                |  |
| Wound complication                             |                |                  |  |
| subjects affected / exposed                    | 1 / 42 (2.38%) | 1 / 261 (0.38%)  |  |
| occurrences (all)                              | 1              | 1                |  |
| Cardiac disorders                              |                |                  |  |
| Palpitations                                   |                |                  |  |
| subjects affected / exposed                    | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)                              | 0              | 0                |  |
| Sinus tachycardia                              |                |                  |  |

|                             |                 |                  |  |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 1 / 42 (2.38%)  | 6 / 261 (2.30%)  |  |
| occurrences (all)           | 1               | 6                |  |
| Tachycardia                 |                 |                  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  | 5 / 261 (1.92%)  |  |
| occurrences (all)           | 1               | 5                |  |
| Nervous system disorders    |                 |                  |  |
| Amnesia                     |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 3 / 261 (1.15%)  |  |
| occurrences (all)           | 0               | 3                |  |
| Aphasia                     |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)  |  |
| occurrences (all)           | 0               | 0                |  |
| Dizziness                   |                 |                  |  |
| subjects affected / exposed | 3 / 42 (7.14%)  | 23 / 261 (8.81%) |  |
| occurrences (all)           | 4               | 24               |  |
| Dysarthria                  |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)  |  |
| occurrences (all)           | 0               | 1                |  |
| Dysgeusia                   |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 2 / 261 (0.77%)  |  |
| occurrences (all)           | 0               | 2                |  |
| Headache                    |                 |                  |  |
| subjects affected / exposed | 5 / 42 (11.90%) | 22 / 261 (8.43%) |  |
| occurrences (all)           | 5               | 24               |  |
| Hypoaesthesia               |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 3 / 261 (1.15%)  |  |
| occurrences (all)           | 0               | 3                |  |
| Lethargy                    |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)  |  |
| occurrences (all)           | 0               | 0                |  |
| Loss of consciousness       |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)  |  |
| occurrences (all)           | 0               | 0                |  |
| Neuralgia                   |                 |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)  |  |
| occurrences (all)           | 0               | 1                |  |

|   |                        |                         |  |
|---|------------------------|-------------------------|--|
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 42 (0.00%)<br>0    | 1 / 261 (0.38%)<br>1    |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 42 (2.38%)<br>1    | 6 / 261 (2.30%)<br>6    |  |
| Paralysis<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 42 (0.00%)<br>0    | 1 / 261 (0.38%)<br>1    |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)             | 1 / 42 (2.38%)<br>1    | 3 / 261 (1.15%)<br>3    |  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 42 (0.00%)<br>0    | 1 / 261 (0.38%)<br>1    |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 42 (0.00%)<br>0    | 2 / 261 (0.77%)<br>3    |  |
| Taste disorder<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 42 (0.00%)<br>0    | 1 / 261 (0.38%)<br>1    |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 42 (0.00%)<br>0    | 0 / 261 (0.00%)<br>0    |  |
| Blood and lymphatic system disorders  |                        |                         |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                   | 11 / 42 (26.19%)<br>13 | 54 / 261 (20.69%)<br>65 |  |
| Disseminated intravascular<br>coagulation<br>subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0    | 0 / 261 (0.00%)<br>0    |  |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 42 (0.00%)<br>0    | 0 / 261 (0.00%)<br>0    |  |
| Iron deficiency anaemia   |                        |                         |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Leukocytosis                |                |                 |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 261 (0.38%) |  |
| occurrences (all)           | 1              | 1               |  |
| Leukopenia                  |                |                 |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 261 (0.77%) |  |
| occurrences (all)           | 0              | 2               |  |
| Lymph node pain             |                |                 |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Lymphopenia                 |                |                 |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 7 / 261 (2.68%) |  |
| occurrences (all)           | 1              | 7               |  |
| Neutropenia                 |                |                 |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 261 (0.77%) |  |
| occurrences (all)           | 1              | 2               |  |
| Thrombocytopenia            |                |                 |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 6 / 261 (2.30%) |  |
| occurrences (all)           | 1              | 8               |  |
| Ear and labyrinth disorders |                |                 |  |
| Hypoacusis                  |                |                 |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences (all)           | 0              | 1               |  |
| Otorrhoea                   |                |                 |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Vertigo                     |                |                 |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 261 (1.15%) |  |
| occurrences (all)           | 1              | 3               |  |
| Eye disorders               |                |                 |  |
| Periorbital oedema          |                |                 |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Photopsia                   |                |                 |  |

|                             |                 |                   |  |
|-----------------------------|-----------------|-------------------|--|
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)           | 0               | 0                 |  |
| Vision blurred              |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)           | 0               | 2                 |  |
| Gastrointestinal disorders  |                 |                   |  |
| Abdominal discomfort        |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)           | 0               | 0                 |  |
| Abdominal distension        |                 |                   |  |
| subjects affected / exposed | 1 / 42 (2.38%)  | 4 / 261 (1.53%)   |  |
| occurrences (all)           | 1               | 4                 |  |
| Abdominal pain              |                 |                   |  |
| subjects affected / exposed | 3 / 42 (7.14%)  | 18 / 261 (6.90%)  |  |
| occurrences (all)           | 3               | 18                |  |
| Abdominal pain lower        |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Abdominal pain upper        |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 4 / 261 (1.53%)   |  |
| occurrences (all)           | 0               | 4                 |  |
| Ascites                     |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)           | 0               | 2                 |  |
| Autoimmune colitis          |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)           | 0               | 0                 |  |
| Constipation                |                 |                   |  |
| subjects affected / exposed | 5 / 42 (11.90%) | 38 / 261 (14.56%) |  |
| occurrences (all)           | 5               | 40                |  |
| Diarrhoea                   |                 |                   |  |
| subjects affected / exposed | 8 / 42 (19.05%) | 37 / 261 (14.18%) |  |
| occurrences (all)           | 13              | 69                |  |
| Dry mouth                   |                 |                   |  |
| subjects affected / exposed | 3 / 42 (7.14%)  | 10 / 261 (3.83%)  |  |
| occurrences (all)           | 3               | 10                |  |

|                                  |                 |                   |
|----------------------------------|-----------------|-------------------|
| Dyspepsia                        |                 |                   |
| subjects affected / exposed      | 1 / 42 (2.38%)  | 7 / 261 (2.68%)   |
| occurrences (all)                | 1               | 7                 |
| Dysphagia                        |                 |                   |
| subjects affected / exposed      | 5 / 42 (11.90%) | 8 / 261 (3.07%)   |
| occurrences (all)                | 5               | 8                 |
| Flatulence                       |                 |                   |
| subjects affected / exposed      | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |
| occurrences (all)                | 0               | 0                 |
| Gastrooesophageal reflux disease |                 |                   |
| subjects affected / exposed      | 0 / 42 (0.00%)  | 2 / 261 (0.77%)   |
| occurrences (all)                | 0               | 2                 |
| Mouth haemorrhage                |                 |                   |
| subjects affected / exposed      | 1 / 42 (2.38%)  | 1 / 261 (0.38%)   |
| occurrences (all)                | 1               | 1                 |
| Mouth ulceration                 |                 |                   |
| subjects affected / exposed      | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |
| occurrences (all)                | 0               | 1                 |
| Nausea                           |                 |                   |
| subjects affected / exposed      | 2 / 42 (4.76%)  | 45 / 261 (17.24%) |
| occurrences (all)                | 2               | 49                |
| Pancreatic duct dilatation       |                 |                   |
| subjects affected / exposed      | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |
| occurrences (all)                | 0               | 0                 |
| Rectal haemorrhage               |                 |                   |
| subjects affected / exposed      | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |
| occurrences (all)                | 0               | 0                 |
| Stomatitis                       |                 |                   |
| subjects affected / exposed      | 1 / 42 (2.38%)  | 6 / 261 (2.30%)   |
| occurrences (all)                | 1               | 7                 |
| Toothache                        |                 |                   |
| subjects affected / exposed      | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |
| occurrences (all)                | 0               | 1                 |
| Vomiting                         |                 |                   |
| subjects affected / exposed      | 3 / 42 (7.14%)  | 32 / 261 (12.26%) |
| occurrences (all)                | 4               | 42                |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Hepatobiliary disorders                    |                |                 |  |
| Cholecystitis                              |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Hyperbilirubinaemia                        |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 1 / 261 (0.38%) |  |
| occurrences (all)                          | 0              | 1               |  |
| Skin and subcutaneous tissue disorders     |                |                 |  |
| Alopecia                                   |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Cold sweat                                 |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Dermatitis acneiform                       |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Dermatitis contact                         |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Erythema                                   |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 4 / 261 (1.53%) |  |
| occurrences (all)                          | 0              | 4               |  |
| Hyperhidrosis                              |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 4 / 261 (1.53%) |  |
| occurrences (all)                          | 0              | 4               |  |
| Lichen planus                              |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Night sweats                               |                |                 |  |
| subjects affected / exposed                | 1 / 42 (2.38%) | 4 / 261 (1.53%) |  |
| occurrences (all)                          | 1              | 4               |  |
| Pain of skin                               |                |                 |  |
| subjects affected / exposed                | 0 / 42 (0.00%) | 0 / 261 (0.00%) |  |
| occurrences (all)                          | 0              | 0               |  |
| Palmar-plantar erythrodysesthesia syndrome |                |                 |  |

|                             |                 |                   |  |
|-----------------------------|-----------------|-------------------|--|
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)           | 0               | 0                 |  |
| Papule                      |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)           | 0               | 0                 |  |
| Pruritus                    |                 |                   |  |
| subjects affected / exposed | 5 / 42 (11.90%) | 27 / 261 (10.34%) |  |
| occurrences (all)           | 6               | 31                |  |
| Rash                        |                 |                   |  |
| subjects affected / exposed | 3 / 42 (7.14%)  | 20 / 261 (7.66%)  |  |
| occurrences (all)           | 3               | 23                |  |
| Rash erythematous           |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Rash maculo-papular         |                 |                   |  |
| subjects affected / exposed | 1 / 42 (2.38%)  | 7 / 261 (2.68%)   |  |
| occurrences (all)           | 1               | 10                |  |
| Skin ulcer                  |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Vitiligo                    |                 |                   |  |
| subjects affected / exposed | 1 / 42 (2.38%)  | 11 / 261 (4.21%)  |  |
| occurrences (all)           | 1               | 11                |  |
| Renal and urinary disorders |                 |                   |  |
| Acute kidney injury         |                 |                   |  |
| subjects affected / exposed | 1 / 42 (2.38%)  | 3 / 261 (1.15%)   |  |
| occurrences (all)           | 1               | 3                 |  |
| Azotaemia                   |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)           | 0               | 0                 |  |
| Dysuria                     |                 |                   |  |
| subjects affected / exposed | 1 / 42 (2.38%)  | 5 / 261 (1.92%)   |  |
| occurrences (all)           | 1               | 8                 |  |
| Haematuria                  |                 |                   |  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)           | 0               | 1                 |  |



|   |                      |                         |  |
|---|----------------------|-------------------------|--|
| Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0  | 0 / 261 (0.00%)<br>0    |  |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 0 / 42 (0.00%)<br>0  | 0 / 261 (0.00%)<br>0    |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)   | 0 / 42 (0.00%)<br>0  | 1 / 261 (0.38%)<br>1    |  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0  | 1 / 261 (0.38%)<br>1    |  |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 42 (2.38%)<br>1  | 13 / 261 (4.98%)<br>13  |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)  | 2 / 42 (4.76%)<br>2  | 17 / 261 (6.51%)<br>18  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 6 / 42 (14.29%)<br>6 | 27 / 261 (10.34%)<br>29 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 5 / 42 (11.90%)<br>6 | 27 / 261 (10.34%)<br>32 |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 42 (0.00%)<br>0  | 8 / 261 (3.07%)<br>10   |  |
| Coccydynia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0  | 0 / 261 (0.00%)<br>0    |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0  | 4 / 261 (1.53%)<br>4    |  |
| Groin pain  |                      |                         |  |

|                             |                |                  |  |
|-----------------------------|----------------|------------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 261 (0.77%)  |  |
| occurrences (all)           | 0              | 2                |  |
| Limb discomfort             |                |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)           | 0              | 0                |  |
| Muscle spasms               |                |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 4 / 261 (1.53%)  |  |
| occurrences (all)           | 0              | 4                |  |
| Muscular weakness           |                |                  |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 10 / 261 (3.83%) |  |
| occurrences (all)           | 2              | 11               |  |
| Musculoskeletal chest pain  |                |                  |  |
| subjects affected / exposed | 2 / 42 (4.76%) | 8 / 261 (3.07%)  |  |
| occurrences (all)           | 2              | 8                |  |
| Musculoskeletal pain        |                |                  |  |
| subjects affected / exposed | 3 / 42 (7.14%) | 19 / 261 (7.28%) |  |
| occurrences (all)           | 3              | 25               |  |
| Myalgia                     |                |                  |  |
| subjects affected / exposed | 3 / 42 (7.14%) | 13 / 261 (4.98%) |  |
| occurrences (all)           | 3              | 15               |  |
| Neck pain                   |                |                  |  |
| subjects affected / exposed | 4 / 42 (9.52%) | 10 / 261 (3.83%) |  |
| occurrences (all)           | 4              | 10               |  |
| Osteoarthritis              |                |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)           | 0              | 0                |  |
| Pain in extremity           |                |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 12 / 261 (4.60%) |  |
| occurrences (all)           | 0              | 13               |  |
| Pathological fracture       |                |                  |  |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |  |
| occurrences (all)           | 0              | 0                |  |
| Infections and infestations |                |                  |  |
| Abdominal infection         |                |                  |  |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 261 (0.38%)  |  |
| occurrences (all)           | 1              | 1                |  |

|                               |                |                  |
|-------------------------------|----------------|------------------|
| Acute sinusitis               |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |
| occurrences (all)             | 0              | 2                |
| Bacteraemia                   |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |
| occurrences (all)             | 0              | 0                |
| Fungal skin infection         |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |
| occurrences (all)             | 0              | 1                |
| Influenza                     |                |                  |
| subjects affected / exposed   | 1 / 42 (2.38%) | 6 / 261 (2.30%)  |
| occurrences (all)             | 1              | 6                |
| Laryngitis bacterial          |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |
| occurrences (all)             | 0              | 0                |
| Nasopharyngitis               |                |                  |
| subjects affected / exposed   | 2 / 42 (4.76%) | 6 / 261 (2.30%)  |
| occurrences (all)             | 3              | 8                |
| Oral candidiasis              |                |                  |
| subjects affected / exposed   | 1 / 42 (2.38%) | 3 / 261 (1.15%)  |
| occurrences (all)             | 1              | 4                |
| Otitis media                  |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |
| occurrences (all)             | 0              | 0                |
| Peritonitis                   |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 0 / 261 (0.00%)  |
| occurrences (all)             | 0              | 0                |
| Pneumonia                     |                |                  |
| subjects affected / exposed   | 3 / 42 (7.14%) | 10 / 261 (3.83%) |
| occurrences (all)             | 3              | 12               |
| Postoperative wound infection |                |                  |
| subjects affected / exposed   | 0 / 42 (0.00%) | 1 / 261 (0.38%)  |
| occurrences (all)             | 0              | 1                |
| Rhinitis                      |                |                  |
| subjects affected / exposed   | 1 / 42 (2.38%) | 1 / 261 (0.38%)  |
| occurrences (all)             | 1              | 1                |

|                                    |                 |                   |  |
|------------------------------------|-----------------|-------------------|--|
| Sinusitis                          |                 |                   |  |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)                  | 0               | 1                 |  |
| Upper respiratory tract infection  |                 |                   |  |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 13 / 261 (4.98%)  |  |
| occurrences (all)                  | 0               | 14                |  |
| Urinary tract infection            |                 |                   |  |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 7 / 261 (2.68%)   |  |
| occurrences (all)                  | 0               | 10                |  |
| Metabolism and nutrition disorders |                 |                   |  |
| Cachexia                           |                 |                   |  |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 1 / 261 (0.38%)   |  |
| occurrences (all)                  | 0               | 1                 |  |
| Decreased appetite                 |                 |                   |  |
| subjects affected / exposed        | 5 / 42 (11.90%) | 60 / 261 (22.99%) |  |
| occurrences (all)                  | 6               | 68                |  |
| Dehydration                        |                 |                   |  |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 2 / 261 (0.77%)   |  |
| occurrences (all)                  | 1               | 2                 |  |
| Diabetes mellitus                  |                 |                   |  |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 3 / 261 (1.15%)   |  |
| occurrences (all)                  | 0               | 4                 |  |
| Hypercalcaemia                     |                 |                   |  |
| subjects affected / exposed        | 3 / 42 (7.14%)  | 9 / 261 (3.45%)   |  |
| occurrences (all)                  | 5               | 12                |  |
| Hyperglycaemia                     |                 |                   |  |
| subjects affected / exposed        | 2 / 42 (4.76%)  | 11 / 261 (4.21%)  |  |
| occurrences (all)                  | 3               | 16                |  |
| Hyperkalaemia                      |                 |                   |  |
| subjects affected / exposed        | 1 / 42 (2.38%)  | 4 / 261 (1.53%)   |  |
| occurrences (all)                  | 1               | 5                 |  |
| Hypernatraemia                     |                 |                   |  |
| subjects affected / exposed        | 0 / 42 (0.00%)  | 0 / 261 (0.00%)   |  |
| occurrences (all)                  | 0               | 0                 |  |
| Hyperphosphataemia                 |                 |                   |  |

|                             |                 |                  |
|-----------------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 42 (0.00%)  | 1 / 261 (0.38%)  |
| occurrences (all)           | 0               | 1                |
| Hyperuricaemia              |                 |                  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)  |
| occurrences (all)           | 0               | 0                |
| Hypoalbuminaemia            |                 |                  |
| subjects affected / exposed | 2 / 42 (4.76%)  | 14 / 261 (5.36%) |
| occurrences (all)           | 2               | 26               |
| Hypocalcaemia               |                 |                  |
| subjects affected / exposed | 5 / 42 (11.90%) | 8 / 261 (3.07%)  |
| occurrences (all)           | 6               | 10               |
| Hypoglycaemia               |                 |                  |
| subjects affected / exposed | 0 / 42 (0.00%)  | 0 / 261 (0.00%)  |
| occurrences (all)           | 0               | 0                |
| Hypokalaemia                |                 |                  |
| subjects affected / exposed | 4 / 42 (9.52%)  | 17 / 261 (6.51%) |
| occurrences (all)           | 11              | 27               |
| Hypomagnesaemia             |                 |                  |
| subjects affected / exposed | 3 / 42 (7.14%)  | 10 / 261 (3.83%) |
| occurrences (all)           | 4               | 14               |
| Hyponatraemia               |                 |                  |
| subjects affected / exposed | 3 / 42 (7.14%)  | 14 / 261 (5.36%) |
| occurrences (all)           | 3               | 14               |
| Hypophosphataemia           |                 |                  |
| subjects affected / exposed | 2 / 42 (4.76%)  | 11 / 261 (4.21%) |
| occurrences (all)           | 2               | 27               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 23 March 2015     | Reduced the starting dose of spartalizumab to 1 mg/kg administered once every two weeks, as requested by a regulatory authority.  |
| 15 June 2015      | <p>Phase II part of the study was to focus specifically on subjects with NSCLC, melanoma and TNBC; the planned expansion groups for subjects with gastric and esophageal cancer, colorectal cancer and anal cancer were removed. Removal of the gastric/esophageal, colorectal and anal cancer groups also affects the role of the PD-L1 biomarker, which was an inclusion criterion for these subjects.</p> <p>No molecular screening for PD-L1 was performed to select subjects however PD-L1 expression was assessed retrospectively for all subjects.</p> <p>At the time of RP2D/MTD determination, the amount of efficacy data collected would be limited. To provide greater confidence in choosing the most appropriate dose for further development, the study design was updated to allow testing of two doses of spartalizumab in one disease indication during the Phase II part.</p> <p>In addition, collection of a sample for cytokine assessment (IL-6 and IFN-<math>\gamma</math>) was added for all subjects at Screening.</p> <p>The wording in prohibited concomitant therapy related to the use of systemic steroid therapy during the course of study was adjusted in order to provide more flexibility for subjects who would need such therapy for treatment of acute conditions.</p> <p>In order to align the collection and analysis of pharmacodynamic biomarkers with preclinical evidence on the timing of immune response in tumor after therapy with PD-1 blocking antibodies, the collection of the on-treatment new tumor biopsy sample was moved from C2D1 (i.e. between C2D1 and C2D15) to C3D1 (i.e. between C3D1 and C3D15).</p>  |
| 19 September 2015 | <p>Restricting subjects with NSCLC to no more than one prior platinum-based doublet chemotherapy regimen, with the exception of subjects with ALK or EGFR-positive disease who were treated with a relevant tyrosine kinase inhibitor and a platinum-based doublet chemotherapy regimen. For subjects with melanoma, all subjects must have developed progressive disease after at least one systemic treatment regimen (for those with BRAF-wild type disease) or one systemic treatment regimen and a BRAF inhibitor (for those with BRAF-mutant disease). No disease-specific limitations were required for subjects with TNBC.</p> <p>Subjects who had previously received a PD-1 or PD-L1 checkpoint inhibitor were excluded from participating; those who had previously received other anticancer immunotherapies such as CTLA-4-directed therapy were eligible.</p> <p>Allowed the testing of a fixed/flat dose of spartalizumab in the phase II part of the study.</p> <p>The use of a fixed/flat dose would reduce the risk of dosing errors and reduce drug product wastage.</p> <p>The requirement that subjects have disease that could be biopsied and be willing to undergo biopsy during the Phase II part of the study was adjusted to allow exceptions after documented discussion with Novartis. This amendment also introduced the possibility to stop the collection of biopsies, once a sufficient number of paired biopsies had been collected.</p> <p>Allowed the collection of tumor tissue upon the development of acquired resistance to treatment.</p> <p>Based on preliminary PK data and the possibility of delayed appearance of immune-related adverse events, the safety follow-up period was extended to 90 days after the last dose of study treatment.</p> <p>Exclusion criteria were updated to exclude sexually active male subjects who were not willing to use a condom during the study.</p> |

|                   |  |
|-------------------|--|
| 13 May 2016       | <p>n the Phase II part. This regimen was to be tested in addition to the RP2D of 400 mg Q4W. Subjects with melanoma were no longer required to have received systemic therapy prior to being eligible for treatment with spartalizumab. All subjects with BRAF V600 mutant melanoma must have received a BRAF inhibitor. Subjects with NSCLC could have received no more than one prior platinum-based doublet therapy. For NSCLC, the subjects with EGFR mutation-positive disease were excluded as the published data suggest these subjects receive limited benefit from treatment with single agent PD-1 inhibitors (Borghaei et al 2015). Subjects with ALK translocation-positive NSCLC were eligible, as the currently available published dataset for these subjects treated with PD-1 inhibitors is limited. A group of subjects was added with anaplastic thyroid cancer in the Phase II part. This was an exploratory group for a type of cancer without effective treatment options. Exclusion criteria was updated to exclude subjects with electrolyte abnormalities &gt; CTCAE grade 2 and a washout period of 4 weeks was required only for live vaccines and to exclude subjects who may not comply with the study for nonmedical reasons. The ECOG performance inclusion criterion was changed to <math>\leq 1</math>. The inclusion criteria of the Phase II part of the study required that the status was known for EGFR (and ALK if EGFR mutation-negative) for subjects with NSCLC, and for BRAF V600 for subjects with melanoma; included the determination of molecular parameters (EGFR, ALK, or BRAF V600 mutational status) at molecular pre-screening by a local laboratory, or by a Novartis-designated laboratory if a local laboratory test was not feasible, for subjects with a tumor of unknown status. Prohibited concomitant therapy section was updated to allow localized radiotherapy for non-target lesions</p> |
| 30 September 2016 | <p>Increased the duration of contraception and safety follow-up periods post spartalizumab treatment from 90 days to 150 days, using five times the upper limit of the half-life of 23 days and an added safety margin. These changes were related to an Urgent Safety Measure communicated on 08-Jun-2016 to all Investigators. With the available PK data obtained from this study an exploratory population PK (PopPK) analysis showed that the T1/2 of spartalizumab in man is 20 [17, 23] days (mean [90% CI]). Many subjects were most likely start a new antineoplastic therapy during the 150 day safety follow-up. Therefore, after the start of a new antineoplastic therapy during the safety follow-up, only AEs and SAEs suspected to be related to spartalizumab were collected in order to focus on the collection of information relevant to spartalizumab; and concomitant medications were recorded until the 30-day safety follow-up or the start of new antineoplastic, whatever occurred first.</p> <p>This amendment also includes new blood samples for PK and PD assays to assess RO in blood and pathway modulation in peripheral blood by analysis of circulating humoral factors and cell based markers (e.g. RNA profiling and FACS analysis of PBMC). RO samples were collected at Day1 of Cycles 1, 3 and 6 and at EoT. In addition RO and PK samples were collected 150 days after last dose. RO samples were collected from all subjects. For pharmacodynamics plasma and PBMCs were collected at Cycle 1 Day 1, Cycle 1 Day15, Cycle 3 Day 1 and 150 days after last dose.</p>  |

|              |   |
|--------------|---|
| 27 July 2017 | Removed the requirement for progression on prior therapy for subjects with ATC; subjects were no longer required to have received therapy prior to being eligible for treatment with spartalizumab. Outcomes for subjects with this disease are dismal with a median life expectancy after diagnosis of less than six months. Given the poor outcome after standard therapy current NCCN treatment guidelines recommend that all subjects be considered for clinical studies. The inclusion criteria was revised in this amendment to allow treatment earlier in the disease course. Specific changes to inclusion criterion #4 for subjects with ATC included: - Subjects were not required to have received or progressed on a prior therapy. - Subjects must not be at short term risk for life threatening complications (such as airway compromise or bleeding from locoregional or metastatic disease). - Chemoradiation and/or surgery was to be considered prior to study entry for those subjects with locally advanced Mutations affecting BRAF occur in approximately 11% - 27% of subjects with ATC. To facilitate a more complete understanding of the subject population benefiting from treatment with spartalizumab, tumor samples were to be tested to determine BRAF V600 mutational status. Knowledge of the BRAF mutation status was not required for study entry. ECG collection was needed only at Screening and as clinically indicated. Prohibited concomitant therapy was modified to better align with medical practice in immuno-oncology. Prohibited concomitant therapy was modified to better align with medical practice in immuno-oncology. Separate primary analyses and indication-specific complete clinical study reports could be provided for this study. Therefore, the protocol was amended to allow separate primary analyses. |
| 16 July 2018 | Incorporated health authority-requested language requiring study treatment discontinuation in the event of Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).<br>Revised to align with recently published guidelines on the clinical management of suspected immune-related toxicities.<br>Removed the use of condom for male study participants receiving spartalizumab. Receptor occupancy and pharmacodynamic (PBMCs and cytokines) samples for markers were no longer to be collected post first primary CSR data cut-off.<br>Language was updated for irRC assessment to clarify criteria for new measurable lesions and irRC response in case of only non-measurable disease at baseline.<br>Removed the reporting of total dose per cycle from statistical section. More details and clarifications were added for reporting other secondary efficacy objectives.<br>Modifications were made to follow Novartis analysis standards safety.   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/#/>

Notes: