



## Clinical trial results:

**A three year extension study to evaluate the long term efficacy, safety and**

**tolerability of secukinumab in subjects with active psoriatic arthritis**

### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2013-001241-13          |
| Trial protocol           | IT GB CZ DE PL BG BE SK |
| Global end of trial date | 11 January 2018         |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 26 January 2019 |
| First version publication date | 26 January 2019 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CAIN457F2306E1 |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01892436 |
| 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                       | 11 January 2018 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 11 January 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the long term efficacy of secukinumab with respect to ACR20, ACR50 and ACR70 response over time up to Week 260 in patients with active PsA who completed the Phase 3 core study CAIN457F2306

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                          | 30 September 2013 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 27          |
| Country: Number of subjects enrolled | Australia: 21          |
| Country: Number of subjects enrolled | Belgium: 6             |
| Country: Number of subjects enrolled | Brazil: 16             |
| Country: Number of subjects enrolled | Bulgaria: 12           |
| Country: Number of subjects enrolled | Canada: 24             |
| Country: Number of subjects enrolled | Czech Republic: 44     |
| Country: Number of subjects enrolled | Germany: 48            |
| Country: Number of subjects enrolled | Israel: 35             |
| Country: Number of subjects enrolled | Italy: 22              |
| Country: Number of subjects enrolled | Philippines: 66        |
| Country: Number of subjects enrolled | Poland: 23             |
| Country: Number of subjects enrolled | Romania: 4             |
| Country: Number of subjects enrolled | Russian Federation: 40 |
| Country: Number of subjects enrolled | Singapore: 16          |
| Country: Number of subjects enrolled | Slovakia: 2            |
| Country: Number of subjects enrolled | Thailand: 30           |
| Country: Number of subjects enrolled | United Kingdom: 37     |
| Country: Number of subjects enrolled | United States: 133     |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 606 |
| EEA total number of subjects       | 198 |

Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| 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)                      | 552 |
| From 65 to 84 years                       | 54  |
| 85 years and over                         | 0   |

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## Subject disposition

### Recruitment

Recruitment details:

The extension FAS (N=457) comprised all patients enrolled in the extension with at least 1 post baseline efficacy assessment during the extension study. 3 patients signed the ICF but had no efficacy assessments during the extension study and were not included in extension FAS.

### Pre-assignment

Screening details:

Of the 457 patients in the extension FAS, 380 (83.2%) completed 260 weeks of treatment (84.4% in the secukinumab 10 mg/kg-75 mg group, 82.0% in the secukinumab 10 mg/kg-150 mg group, 85.1% in the placebo-secukinumab 75 mg group and 81.3% in the placebo-secukinumab 150 mg group)

### Period 1

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

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Secukinumab 75mg |

Arm description:

Subjects continued to receive secukinumab 75mg in PFS (same dose as that was received in core study CAIN457F2306) every 4 weeks up to Week 256. From Week 156, patients may have been escalated to 150 mg or 300 mg as judged appropriate by investigator

|                                        |                                             |
|----------------------------------------|---------------------------------------------|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | secukinumab                                 |
| Investigational medicinal product code | AIN457F                                     |
| Other name                             |                                             |
| Pharmaceutical forms                   | Solution for infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                            |

Dosage and administration details:

75 mg

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Secukinumab 150mg |
|------------------|-------------------|

Arm description:

Subjects continued to receive secukinumab 150mg in PFS (same dose as that was received in core study CAIN457F2306) every 4 weeks up to Week 256. From Week 156, patients may have been escalated to 300 mg as judged appropriate by the investigator

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | secukinumab            |
| Investigational medicinal product code | AIN457F                |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

150 MG

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Placebo - AIN457A 75mg |
|------------------|------------------------|

Arm description:

Placebo (for maintaining the blind till Week 152): Placebo to secukinumab .05 mL solution for injection was provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contained a mixture of inactive excipients, matching the composition of secukinumab 75mg. Participants also

received secukinumab 75mg from week 16/24. Patients may have been escalated to 150 mg or 300 mg as judged appropriate by investigator

|                                        |                                              |
|----------------------------------------|----------------------------------------------|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | placebo                                      |
| Investigational medicinal product code |                                              |
| Other name                             |                                              |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |
| Dosage and administration details:     |                                              |
| 75 mg                                  |                                              |
| <b>Arm title</b>                       | Placebo - AIN457 150mg                       |

Arm description:

Placebo (for maintaining the blind till Week 152): Placebo to secukinumab 0.5mL solution for injection was provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contained a mixture of inactive excipients, matching the composition of secukinumab 150 mg. Participants also received secukinumab 150 mg from week 16/24. patients may have been escalated to 300mg or 300 mg as judged appropriate by investigator

|                                        |                                             |
|----------------------------------------|---------------------------------------------|
| Arm type                               | Placebo                                     |
| Investigational medicinal product name | placebo                                     |
| Investigational medicinal product code |                                             |
| Other name                             |                                             |
| Pharmaceutical forms                   | Solution for infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                            |

Dosage and administration details:

150 mg

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Secukinumab 75mg | Secukinumab 150mg | Placebo - AIN457A 75mg |
|-----------------------------------------------------|------------------|-------------------|------------------------|
| Started                                             | 147              | 161               | 74                     |
| Completed                                           | 124              | 132               | 63                     |
| Not completed                                       | 23               | 29                | 11                     |
| Adverse event, serious fatal                        | 1                | 1                 | -                      |
| Consent withdrawn by subject                        | 8                | 15                | 4                      |
| Physician decision                                  | 2                | 1                 | -                      |
| non-compliance with treatment                       | 1                | -                 | -                      |
| Adverse event, non-fatal                            | 7                | 6                 | 2                      |
| Technical problems                                  | 2                | 1                 | 1                      |
| Pregnancy                                           | -                | 2                 | 1                      |
| Lost to follow-up                                   | 1                | 1                 | 1                      |
| Lack of efficacy                                    | 1                | 2                 | 2                      |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo - AIN457 150mg |
|-----------------------------------------------------|------------------------|
| Started                                             | 75                     |
| Completed                                           | 61                     |
| Not completed                                       | 14                     |

|                               |   |
|-------------------------------|---|
| Adverse event, serious fatal  | - |
| Consent withdrawn by subject  | 4 |
| Physician decision            | 1 |
| non-compliance with treatment | - |
| Adverse event, non-fatal      | 3 |
| Technical problems            | 1 |
| Pregnancy                     | - |
| Lost to follow-up             | 3 |
| Lack of efficacy              | 2 |

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Notes:

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

Justification: Of the 457 patients in the extension FAS, 380 (83.2%) completed 260 weeks of treatment (84.4% in the secukinumab 10 mg/kg-75 mg group, 82.0% in the secukinumab 10 mg/kg-150 mg group, 85.1% in the placebo-secukinumab 75 mg group and 81.3% in the placebo-secukinumab 150 mg group)

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secukinumab 75mg       |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                        |
| Subjects continued to receive secukinumab 75mg in PFS (same dose as that was received in core study CAIN457F2306) every 4 weeks up to Week 256. From Week 156, patients may have been escalated to 150 mg or 300 mg as judged appropriate by investigator                                                                                                                                                                                                    |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secukinumab 150mg      |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                        |
| Subjects continued to receive secukinumab 150mg in PFS (same dose as that was received in core study CAIN457F2306) every 4 weeks up to Week 256. From Week 156, patients may have been escalated to 300 mg as judged appropriate by the investigator                                                                                                                                                                                                         |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                        | Placebo - AIN457A 75mg |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                        |
| Placebo (for maintaining the blind till Week 152): Placebo to secukinumab .05 mL solution for injection was provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contained a mixture of inactive excipients, matching the composition of secukinumab 75mg. Participants also received secukinumab 75mg from week 16/24. Patients may have been escalated to 150 mg or 300 mg as judged appropriate by investigator   |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                        | Placebo - AIN457 150mg |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                        |
| Placebo (for maintaining the blind till Week 152): Placebo to secukinumab 0.5mL solution for injection was provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contained a mixture of inactive excipients, matching the composition of secukinumab 150 mg. Participants also received secukinumab 150 mg from week 16/24. patients may have been escalated to 300mg or 300 mg as judged appropriate by investigator |                        |

| Reporting group values                        | Secukinumab 75mg | Secukinumab 150mg | Placebo - AIN457A 75mg |
|-----------------------------------------------|------------------|-------------------|------------------------|
| Number of subjects                            | 147              | 161               | 74                     |
| Age, Customized<br>Units: Subjects            |                  |                   |                        |
| 18y - <65 y                                   | 132              | 145               | 72                     |
| >=65 y -<85                                   | 15               | 16                | 2                      |
| Age continuous<br>Units: years                |                  |                   |                        |
| arithmetic mean                               | 48.9             | 49.5              | 47.4                   |
| standard deviation                            | ± 11.78          | ± 11.67           | ± 10.64                |
| Sex: Female, Male<br>Units: Subjects          |                  |                   |                        |
| Female                                        | 81               | 83                | 40                     |
| Male                                          | 66               | 78                | 34                     |
| Race/Ethnicity, Customized<br>Units: Subjects |                  |                   |                        |
| White                                         | 118              | 130               | 51                     |
| Black or African American                     | 1                | 1                 | 0                      |
| Asian                                         | 27               | 29                | 23                     |
| Other                                         | 1                | 1                 | 0                      |

| Reporting group values | Placebo - AIN457 150mg | Total |  |
|------------------------|------------------------|-------|--|
| Number of subjects     | 75                     | 457   |  |

|                                               |         |     |  |
|-----------------------------------------------|---------|-----|--|
| Age, Customized<br>Units: Subjects            |         |     |  |
| 18y - <65 y                                   | 71      | 420 |  |
| >=65 y -<85                                   | 4       | 37  |  |
| Age continuous<br>Units: years                |         |     |  |
| arithmetic mean                               | 49.0    |     |  |
| standard deviation                            | ± 11.42 | -   |  |
| Sex: Female, Male<br>Units: Subjects          |         |     |  |
| Female                                        | 38      | 242 |  |
| Male                                          | 37      | 215 |  |
| Race/Ethnicity, Customized<br>Units: Subjects |         |     |  |
| White                                         | 58      | 357 |  |
| Black or African American                     | 0       | 2   |  |
| Asian                                         | 16      | 95  |  |
| Other                                         | 1       | 3   |  |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secukinumab 75mg       |
| Reporting group description:<br>Subjects continued to receive secukinumab 75mg in PFS (same dose as that was received in core study CAIN457F2306) every 4 weeks up to Week 256. From Week 156, patients may have been escalated to 150 mg or 300 mg as judged appropriate by investigator                                                                                                                                                                                                    |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secukinumab 150mg      |
| Reporting group description:<br>Subjects continued to receive secukinumab 150mg in PFS (same dose as that was received in core study CAIN457F2306) every 4 weeks up to Week 256. From Week 156, patients may have been escalated to 300 mg as judged appropriate by the investigator                                                                                                                                                                                                         |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Placebo - AIN457A 75mg |
| Reporting group description:<br>Placebo (for maintaining the blind till Week 152): Placebo to secukinumab .05 mL solution for injection was provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contained a mixture of inactive excipients, matching the composition of secukinumab 75mg. Participants also received secukinumab 75mg from week 16/24. Patients may have been escalated to 150 mg or 300 mg as judged appropriate by investigator   |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Placebo - AIN457 150mg |
| Reporting group description:<br>Placebo (for maintaining the blind till Week 152): Placebo to secukinumab 0.5mL solution for injection was provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contained a mixture of inactive excipients, matching the composition of secukinumab 150 mg. Participants also received secukinumab 150 mg from week 16/24. patients may have been escalated to 300mg or 300 mg as judged appropriate by investigator |                        |

### Primary: Proportion of subject who reached (American College of Rheumatology score of 20) ACR20

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Proportion of subject who reached (American College of Rheumatology score of 20) ACR20 <sup>[1]</sup> |
| End point description:<br>Proportion of subjects with a positive clinical response to treatment (individual improvement) in disease activity according to ACR20 criteria if he/she has at least 20% improvement in 1. Tender 68-joint count 2. Swollen 66-joint count and 3. At least 3 of the following 5 measures: - Patient's assessment of Psoriatic Arthritis (PsA) pain - Patient's global assessment of disease activity - Physician's global assessment of disease activity - Subject self-assessed disability (Health-Assessment Questionnaire [HAQ-DI] score) - Acute phase reactant (hsCRP or ESR) |                                                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Primary                                                                                               |
| End point timeframe:<br>weeks 116, 128, 140, 156, 180, 208, 232 and 260                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                       |

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 WAS PLANNED

| End point values                  | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|-----------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed       | 147                 | 161                 | 74                     | 75                     |
| Units: percentage of participants |                     |                     |                        |                        |
| number (confidence interval 95%)  |                     |                     |                        |                        |
| week 116                          | 71.3 (63.1 to 78.4) | 73.9 (66.0 to 80.5) | 73.2 (61.2 to 82.7)    | 73.6 (61.7 to 83.0)    |

|          |                     |                     |                     |                     |
|----------|---------------------|---------------------|---------------------|---------------------|
| week 128 | 69.7 (61.4 to 77.0) | 72.9 (65.1 to 79.6) | 76.8 (64.8 to 85.8) | 74.6 (62.7 to 83.9) |
| week 140 | 69.8 (61.3 to 77.1) | 71.1 (63.1 to 78.0) | 79.2 (67.7 to 87.5) | 69.4 (57.3 to 79.5) |
| week 156 | 64.3 (55.8 to 72.0) | 76.1 (68.5 to 82.4) | 75.3 (63.6 to 84.4) | 67.6 (55.6 to 77.7) |
| week 180 | 73.0 (64.6 to 80.0) | 72.5 (64.1 to 79.6) | 74.6 (62.3 to 84.1) | 67.7 (54.8 to 78.5) |
| week 208 | 72.8 (64.4 to 79.9) | 66.9 (58.5 to 74.3) | 75.0 (62.8 to 84.4) | 68.2 (55.4 to 78.8) |
| week 232 | 79.5 (71.3 to 86.0) | 69.5 (60.7 to 77.0) | 83.3 (71.7 to 91.0) | 80.3 (67.8 to 89.0) |
| week 260 | 77.2 (68.7 to 83.9) | 67.9 (59.1 to 75.7) | 78.8 (66.7 to 87.5) | 77.4 (64.7 to 86.7) |

## Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of subjects who reached ACR50

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Proportion of subjects who reached ACR50 <sup>[2]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                         |
| Proportion of subjects that have a positive clinical response to treatment (individual improvement) in disease activity according to ACR50 criteria if he/she has at least 50% improvement in 1. Tender 68-joint count 2. Swollen 66-joint count and 3. At least 3 of the following 5 measures: - Patient's assessment of PsA pain - Patient's global assessment of disease activity - Physician's global assessment of disease activity - Subject self-assessed disability (Health-Assessment Questionnaire [HAQ-DI] score) - Acute phase reactant (hsCRP or ESR) |                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary                                                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                         |
| weeks 116, 128, 140, 156, 180, 208, 232 and 260                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                         |

Notes:

[2] - 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 WAS PLANNED

| End point values                  | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|-----------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed       | 147                 | 161                 | 74                     | 75                     |
| Units: percentage of participants |                     |                     |                        |                        |
| number (confidence interval 95%)  |                     |                     |                        |                        |
| week 116                          | 43.4 (35.2 to 51.9) | 51.0 (42.8 to 59.1) | 49.3 (37.3 to 61.3)    | 47.2 (35.5 to 59.3)    |
| week 128                          | 43.7 (35.4 to 52.2) | 52.9 (44.8 to 60.9) | 56.5 (44.1 to 68.2)    | 53.5 (41.4 to 65.3)    |
| week 140                          | 41.7 (33.5 to 50.4) | 48.7 (40.5 to 56.9) | 51.4 (39.4 to 63.2)    | 44.4 (32.9 to 56.6)    |
| week 156                          | 39.2 (31.2 to 47.7) | 56.1 (47.9 to 64.0) | 52.1 (40.1 to 63.8)    | 47.3 (35.7 to 59.2)    |
| week 180                          | 43.1 (34.7 to 51.8) | 45.7 (37.2 to 54.3) | 52.2 (39.8 to 64.4)    | 50.8 (38.2 to 63.3)    |
| week 208                          | 44.9 (36.4 to 53.6) | 46.9 (38.6 to 55.3) | 52.9 (40.5 to 65.0)    | 53.0 (40.4 to 65.3)    |
| week 232                          | 49.6 (40.7 to 58.6) | 53.4 (44.5 to 62.1) | 53.0 (40.4 to 65.3)    | 50.8 (37.8 to 63.7)    |

|          |                     |                     |                     |                     |
|----------|---------------------|---------------------|---------------------|---------------------|
| week 260 | 51.2 (42.2 to 60.1) | 52.7 (43.8 to 61.4) | 60.6 (47.8 to 72.2) | 50.0 (37.2 to 62.8) |
|----------|---------------------|---------------------|---------------------|---------------------|

## Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of subjects who reached ACR70

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Proportion of subjects who reached ACR70 <sup>[3]</sup> |
|-----------------|---------------------------------------------------------|

End point description:

Proportion of subjects that have a positive clinical response to treatment (individual improvement) in disease activity according to ACR70 criteria if he/she has at least 70% improvement in 1. Tender 68-joint count 2. Swollen 66-joint count and 3. At least 3 of the following 5 measures: - Patient's assessment of PsA pain - Patient's global assessment of disease activity - Physician's global assessment of disease activity - Subject self-assessed disability (Health-Assessment Questionnaire [HAQ-DI] score) - Acute phase reactant (hsCRP or ESR)

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

End point timeframe:

weeks 116, 128, 140, 156, 180, 208, 232 and 260

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 WAS PLANNED

| End point values                  | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|-----------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed       | 147                 | 161                 | 74                     | 75                     |
| Units: percentage of participants |                     |                     |                        |                        |
| number (confidence interval 95%)  |                     |                     |                        |                        |
| week 116                          | 23.8 (17.2 to 31.8) | 30.1 (23.1 to 38.1) | 28.2 (18.4 to 40.3)    | 29.2 (19.3 to 41.2)    |
| week 128                          | 24.6 (18.0 to 32.7) | 31.0 (23.9 to 39.0) | 34.8 (24.0 to 47.3)    | 23.9 (14.9 to 35.8)    |
| week 140                          | 27.3 (20.3 to 35.7) | 28.3 (21.4 to 36.3) | 33.3 (22.9 to 45.5)    | 27.8 (18.2 to 39.8)    |
| week 156                          | 25.9 (19.1 to 34.0) | 32.9 (25.7 to 41.0) | 26.0 (16.8 to 37.8)    | 27.0 (17.7 to 38.8)    |
| week 180                          | 27.0 (20.0 to 35.4) | 31.2 (23.7 to 39.7) | 31.3 (20.9 to 44.0)    | 27.7 (17.7 to 40.4)    |
| week 208                          | 25.7 (18.8 to 34.1) | 31.0 (23.8 to 39.3) | 32.4 (21.8 to 44.9)    | 28.8 (18.6 to 41.4)    |
| week 232                          | 35.4 (27.3 to 44.5) | 32.1 (24.3 to 40.9) | 37.9 (26.5 to 50.7)    | 34.4 (23.0 to 47.8)    |
| week 260                          | 33.9 (25.9 to 42.9) | 37.4 (29.2 to 46.3) | 37.9 (26.5 to 50.7)    | 33.9 (22.6 to 47.1)    |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)**

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Changes from baseline in score of the disability assessment component of the HAQ (Health Assessment Questionnaire - Disability Index). The HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities.

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

End point timeframe:

weeks 116, 128, 140, 156, 180, 208, 232 and 260

| End point values                     | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|--------------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed          | 147                 | 161                 | 74                     | 75                     |
| Units: change in scores              |                     |                     |                        |                        |
| arithmetic mean (standard deviation) |                     |                     |                        |                        |
| week 116                             | -0.4537 (± 0.60617) | -0.4592 (± 0.56155) | -0.5642 (± 0.56722)    | -0.4115 (± 0.66721)    |
| week 128                             | -0.4171 (± 0.61192) | -0.4619 (± 0.55835) | -0.5143 (± 0.55599)    | -0.3750 (± 0.69661)    |
| week 140                             | -0.4448 (± 0.61406) | -0.4713 (± 0.58791) | -0.4635 (± 0.56037)    | -0.3507 (± 0.69221)    |
| week 156                             | -0.4236 (± 0.61896) | -0.4266 (± 0.57491) | -0.5068 (± 0.62548)    | -0.3159 (± 0.73507)    |
| week 180                             | -0.4617 (± 0.61472) | -0.4305 (± 0.59901) | -0.5698 (± 0.65258)    | -0.3538 (± 0.71246)    |
| week 208                             | -0.4463 (± 0.57130) | -0.3857 (± 0.59304) | -0.5531 (± 0.62622)    | -0.3447 (± 0.74745)    |
| week 232                             | -0.4710 (± 0.60931) | -0.4122 (± 0.60461) | -0.5777 (± 0.66930)    | -0.3952 (± 0.72115)    |
| week 260                             | -0.4821 (± 0.61170) | -0.4036 (± 0.58334) | -0.5038 (± 0.61039)    | -0.3730 (± 0.71306)    |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Minimal Clinically Important Difference (MCID) in Health Assessment Questionnaire Disability Index (HAQ-DI)**

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Minimal Clinically Important Difference (MCID) in Health Assessment Questionnaire Disability Index (HAQ-DI) |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Percentage of subjects with improvements from baseline in HAQ-DI meeting or exceeding minimal clinically important difference (MCID=0.3). The HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities.

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

End point timeframe:

weeks 116, 128, 140, 156, 180, 208, 232 and 260

| End point values                  | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|-----------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed       | 147                 | 161                 | 74                     | 75                     |
| Units: percentage of participants |                     |                     |                        |                        |
| number (confidence interval 95%)  |                     |                     |                        |                        |
| week 116                          | 53.1 (44.6 to 61.5) | 52.3 (44.1 to 60.4) | 63.9 (51.7 to 74.6)    | 50.0 (38.1 to 61.9)    |
| week 128                          | 52.8 (44.3 to 61.2) | 51.9 (43.8 to 60.0) | 57.1 (44.8 to 68.7)    | 54.9 (42.7 to 66.6)    |
| week 140                          | 55.4 (46.7 to 63.7) | 52.3 (44.1 to 60.4) | 56.9 (44.8 to 68.4)    | 48.6 (36.8 to 60.6)    |
| week 156                          | 52.8 (44.3 to 61.1) | 52.3 (44.1 to 60.3) | 60.8 (48.7 to 71.7)    | 44.6 (33.2 to 56.6)    |
| week 180                          | 56.9 (48.2 to 65.3) | 51.5 (42.8 to 60.1) | 61.2 (48.5 to 72.6)    | 47.7 (35.3 to 60.4)    |
| week 208                          | 53.3 (44.6 to 61.9) | 50.0 (41.6 to 58.4) | 59.4 (46.9 to 70.9)    | 48.5 (36.1 to 61.0)    |
| week 232                          | 55.2 (46.1 to 64.0) | 48.9 (40.1 to 57.7) | 59.1 (46.3 to 70.8)    | 52.5 (39.4 to 65.2)    |
| week 260                          | 55.6 (46.5 to 64.3) | 48.9 (40.1 to 57.7) | 59.1 (46.3 to 70.8)    | 53.2 (40.2 to 65.8)    |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Disease Activity Score-CRP (DAS28)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Change from baseline in Disease Activity Score-CRP (DAS28) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                            |
| Changes in DAS28 (utilizing hsCRP) from baseline to over entire study duration up to Month 60. The DAS28 is a measure of disease activity in PsA based on Swollen and Tender Joint Counts (out of a total of 28), hsCRP and the Patient's Global Assessment of Disease Activity. A DAS28 score greater than 5.1 implies active disease, equal to or less than 3.2 low disease activity, and less than 2.6 remission. This measure represents change in scores - not the actual scores. |                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                            |
| weeks 116, 128, 140, 156, 180, 208, 232 and 260                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                            |

| End point values                     | Secukinumab 75mg  | Secukinumab 150mg | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|--------------------------------------|-------------------|-------------------|------------------------|------------------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group        | Reporting group        |
| Number of subjects analysed          | 147               | 161               | 74                     | 75                     |
| Units: change in scores              |                   |                   |                        |                        |
| arithmetic mean (standard deviation) |                   |                   |                        |                        |
| week 116                             | -2.044 (± 1.3382) | -1.904 (± 1.3165) | -2.282 (± 1.2732)      | -1.853 (± 1.2737)      |

|          |                   |                   |                   |                   |
|----------|-------------------|-------------------|-------------------|-------------------|
| week 128 | -2.013 (± 1.3446) | -1.962 (± 1.2900) | -2.333 (± 1.2815) | -2.031 (± 1.3290) |
| week 140 | -2.074 (± 1.3224) | -1.912 (± 1.2246) | -2.412 (± 1.3059) | -1.830 (± 1.3136) |
| week 156 | -1.844 (± 1.4923) | -1.942 (± 1.3195) | -2.109 (± 1.3188) | -1.743 (± 1.3630) |
| week 180 | -2.058 (± 1.3760) | -1.937 (± 1.2674) | -2.327 (± 1.2339) | -1.867 (± 1.4590) |
| week 208 | -2.042 (± 1.2907) | -1.767 (± 1.4574) | -2.344 (± 1.3351) | -1.862 (± 1.4708) |
| week 232 | -2.225 (± 1.2570) | -2.046 (± 1.2590) | -2.611 (± 1.3247) | -2.286 (± 1.2102) |
| week 260 | -2.112 (± 1.2664) | -2.074 (± 1.3146) | -2.506 (± 1.3774) | -2.099 (± 1.2466) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects achieving low disease activity

|                                                                                                                                                                                                                                                                                                                                                                                           |                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                           | Percentage of subjects achieving low disease activity |
| End point description:                                                                                                                                                                                                                                                                                                                                                                    |                                                       |
| Percentage of subjects achieving low disease activity (DAS28 ≤ 3.2). The DAS28 is a measure of disease activity in PsA based on Swollen and Tender Joint Counts (out of a total of 28), hsCRP and the Patient's Global Assessment of Disease Activity. A DAS28 score greater than 5.1 implies active disease, equal to or less than 3.2 low disease activity, and less than 2.6 remission |                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                            | Secondary                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                      |                                                       |
| weeks 116, 128, 140, 156, 180, 208, 232 and 260                                                                                                                                                                                                                                                                                                                                           |                                                       |

| End point values                  | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|-----------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed       | 147                 | 161                 | 74                     | 75                     |
| Units: percentage of participants |                     |                     |                        |                        |
| number (confidence interval 95%)  |                     |                     |                        |                        |
| week 116                          | 70.3 (62.1 to 77.5) | 64.7 (56.5 to 72.1) | 70.4 (58.2 to 80.4)    | 63.9 (51.7 to 74.6)    |
| week 128                          | 69.5 (61.1 to 76.8) | 69.9 (61.9 to 76.8) | 75.4 (63.3 to 84.6)    | 68.6 (56.2 to 78.9)    |
| week 140                          | 72.9 (64.6 to 79.9) | 66.0 (57.8 to 73.4) | 75.0 (63.2 to 84.1)    | 65.3 (53.1 to 75.9)    |
| week 156                          | 63.4 (54.8 to 71.2) | 67.9 (59.9 to 75.1) | 61.6 (49.5 to 72.6)    | 58.9 (46.8 to 70.1)    |
| week 180                          | 71.2 (62.8 to 78.4) | 70.1 (61.6 to 77.4) | 65.7 (53.0 to 76.6)    | 68.8 (55.8 to 79.4)    |
| week 208                          | 71.7 (63.3 to 78.9) | 65.8 (57.4 to 73.3) | 67.2 (54.5 to 77.9)    | 71.2 (58.6 to 81.4)    |
| week 232                          | 75.2 (66.7 to 82.2) | 73.5 (65.0 to 80.6) | 79.4 (67.0 to 88.1)    | 84.7 (72.5 to 92.4)    |
| week 260                          | 74.4 (65.8 to 81.5) | 75.0 (66.6 to 81.9) | 76.9 (64.5 to 86.1)    | 77.4 (64.7 to 86.7)    |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of subjects achieving disease remission (DAS28<2.6)

|                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                | Percentage of subjects achieving disease remission (DAS28<2.6) |
| End point description:<br>Percentage of subjects achieving disease remission (DAS28<2.6). The DAS28 is a measure of disease activity in PsA based on Swollen and Tender Joint Counts (out of a total of 28), hsCRP and the Patient's Global Assessment of Disease Activity. A DAS28 score greater than 5.1 implies active disease, equal to or less than 3.2 low disease activity, and less than 2.6 remission |                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                                                      |
| End point timeframe:<br>weeks 116, 128, 140, 156, 180, 208, 232 and 260                                                                                                                                                                                                                                                                                                                                        |                                                                |

| End point values                  | Secukinumab 75mg    | Secukinumab 150mg   | Placebo - AIN457A 75mg | Placebo - AIN457 150mg |
|-----------------------------------|---------------------|---------------------|------------------------|------------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group        | Reporting group        |
| Number of subjects analysed       | 147                 | 161                 | 74                     | 75                     |
| Units: percentage of participants |                     |                     |                        |                        |
| number (confidence interval 95%)  |                     |                     |                        |                        |
| week 116                          | 52.4 (44.0 to 60.7) | 50.3 (42.2 to 58.5) | 47.9 (36.0 to 60.0)    | 45.8 (34.2 to 57.9)    |
| week 128                          | 54.6 (46.0 to 62.9) | 49.4 (41.3 to 57.4) | 55.1 (42.7 to 66.9)    | 57.1 (44.8 to 68.7)    |
| week 140                          | 58.6 (49.9 to 66.7) | 46.7 (38.5 to 55.0) | 55.6 (43.4 to 67.1)    | 51.4 (39.4 to 63.2)    |
| week 156                          | 48.6 (40.2 to 57.1) | 52.6 (44.4 to 60.6) | 43.8 (32.4 to 55.9)    | 46.6 (35.0 to 58.6)    |
| week 180                          | 54.7 (46.0 to 63.1) | 53.3 (44.6 to 61.8) | 49.3 (37.0 to 61.6)    | 58.6 (46.2 to 70.0)    |
| week 208                          | 56.5 (47.8 to 64.8) | 52.1 (43.7 to 60.3) | 55.2 (42.6 to 67.2)    | 53.0 (40.4 to 65.3)    |
| week 232                          | 64.3 (55.4 to 72.4) | 61.4 (52.5 to 69.6) | 65.1 (51.9 to 76.4)    | 69.5 (56.0 to 80.5)    |
| week 260                          | 55.0 (46.0 to 63.7) | 58.3 (49.4 to 66.7) | 64.6 (51.7 to 75.8)    | 66.1 (52.9 to 77.4)    |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Any AIN457 150 mg |
|-----------------------|-------------------|

Reporting group description:

Any AIN457 150 mg

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Any AIN457 75 mg |
|-----------------------|------------------|

Reporting group description:

Any AIN457 75 mg

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Any AIN457 300 mg |
|-----------------------|-------------------|

Reporting group description:

Any AIN457 300 mg

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

Reporting group description:

Placebo

| Serious adverse events                                              | Any AIN457 150 mg | Any AIN457 75 mg  | Any AIN457 300 mg |
|---------------------------------------------------------------------|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                   |
| subjects affected / exposed                                         | 97 / 473 (20.51%) | 48 / 292 (16.44%) | 10 / 165 (6.06%)  |
| number of deaths (all causes)                                       | 3                 | 3                 | 0                 |
| number of deaths resulting from adverse events                      | 0                 | 0                 | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Basal cell carcinoma                                                |                   |                   |                   |
| subjects affected / exposed                                         | 1 / 473 (0.21%)   | 1 / 292 (0.34%)   | 0 / 165 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1             | 1 / 1             | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0             |
| Brain neoplasm                                                      |                   |                   |                   |
| subjects affected / exposed                                         | 1 / 473 (0.21%)   | 0 / 292 (0.00%)   | 0 / 165 (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             |
| Breast cancer                                                       |                   |                   |                   |



|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Haemangioma                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Intraductal papilloma of breast                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Intraductal proliferative breast lesion         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive breast carcinoma                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Laryngeal cancer stage 0                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Leiomyosarcoma                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Metastases to bone                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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-small cell lung cancer                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian germ cell teratoma benign               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Phaeochromocytoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleomorphic adenoma                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Schwannoma                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Squamous cell carcinoma of pharynx              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Uterine leiomyoma                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Vascular disorders                              |                 |                 |                 |
| Aortic aneurysm                                 |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Hypertension                                         |                 |                 |                 |
| subjects affected / exposed                          | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Pelvic venous thrombosis                             |                 |                 |                 |
| subjects affected / exposed                          | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Polyarteritis nodosa                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Pregnancy, puerperium and perinatal conditions       |                 |                 |                 |
| Abortion spontaneous                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Impaired healing                                     |                 |                 |                 |
| subjects affected / exposed                          | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all      | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 4 / 473 (0.85%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral swelling                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Adenomyosis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Adnexa uteri cyst                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Endometriosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Menorrhagia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Metrorrhagia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Pelvic adhesions                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Uterine haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Haemothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| 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 alveolar haemorrhage                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 3 / 473 (0.63%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| 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  |                 |                 |                 |
| Cervical vertebral fracture                     |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Comminuted fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Eyelid injury                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Face injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Fall                                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Fibula fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Head injury                                     |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Multiple injuries                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Pelvic fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Periprosthetic osteolysis                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Skin abrasion                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skull fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Sternal fracture                                |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Tibia fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Toxicity to various agents                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Traumatic liver injury                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Ulna fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Wound dehiscence                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute myocardial infarction                     |                 |                 |                 |



|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 2 / 292 (0.68%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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                     | 1 / 473 (0.21%) | 4 / 292 (1.37%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block second degree            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| 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 failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 1 / 292 (0.34%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Coronary artery disease                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Coronary artery insufficiency                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 3 / 292 (1.03%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Myocarditis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Cerebral infarction                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Encephalopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Hemiplegia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Intracranial venous sinus thrombosis            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Syncope                                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Thrombotic stroke                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Haemolytic anaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukocytosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Normocytic anaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo positional                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 2 / 292 (0.68%) | 0 / 165 (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           |
| Eye disorders                                   |                 |                 |                 |
| Ocular myasthenia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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 disorders                      |                 |                 |                 |
| Abdominal adhesions                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aphthous ulcer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Colitis                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Colitis ulcerative                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Crohn's disease                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Diarrhoea haemorrhagic                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Enteritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Femoral hernia                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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 haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Large intestine polyp                           |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Mouth ulceration                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Obstructive pancreatitis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Odynophagia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Oesophagitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Umbilical hernia                                |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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>Hepatobiliary disorders</b>                  |                 |                 |                 |
| Biliary colic                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Chronic hepatitis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Drug-induced liver injury                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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>Skin and subcutaneous tissue disorders</b>   |                 |                 |                 |
| Erythema nodosum                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Rosacea                                         |                 |                 |                 |



|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Ureterolithiasis                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Endocrine disorders                             |                 |                 |                 |
| Basedow's disease                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Goitre                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 2 / 292 (0.68%) | 0 / 165 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 0 / 292 (0.00%) | 0 / 165 (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           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 473 (0.63%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot deformity                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc degeneration                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Limb asymmetry                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 7 / 473 (1.48%) | 3 / 292 (1.03%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteochondrosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in extremity                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 473 (0.42%) | 1 / 292 (0.34%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psoriatic arthropathy                           |                 |                 |                 |
| subjects affected / exposed                     | 5 / 473 (1.06%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rotator cuff syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Scoliosis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Synovitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal sepsis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Abscess limb                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Appendiceal abscess                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Appendicitis                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 1 / 165 (0.61%) |
| 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                     | 4 / 473 (0.85%) | 2 / 292 (0.68%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dengue fever                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Diarrhoea infectious                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 473 (0.63%) | 1 / 292 (0.34%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 1 / 292 (0.34%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Escherichia sepsis                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Escherichia urinary tract infection             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Gastroenteritis                                 |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Intervertebral discitis                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Klebsiella sepsis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Lung abscess                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Necrotising fasciitis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Oesophageal candidiasis                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 4 / 473 (0.85%) | 3 / 292 (1.03%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 3 / 4           | 3 / 3           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Post procedural infection                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Prostatitis Escherichia coli                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Rash pustular                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Salpingo-oophoritis                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Sepsis                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 2 / 292 (0.68%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 2 / 292 (0.68%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 0 / 292 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Streptococcal infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Tonsillitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Typhoid fever                                   |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Upper respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 473 (0.42%) | 1 / 292 (0.34%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection bacterial               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Viral infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Wound infection staphylococcal                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 473 (0.00%) | 1 / 292 (0.34%) | 0 / 165 (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           |
| Hypokalaemia                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 473 (0.21%) | 0 / 292 (0.00%) | 0 / 165 (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>                                       | Placebo          |  |  |
|---------------------------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed                                         | 11 / 202 (5.45%) |  |  |
| number of deaths (all causes)                                       | 0                |  |  |
| number of deaths resulting from adverse events                      | 0                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Basal cell carcinoma                                                |                  |  |  |
| subjects affected / exposed                                         | 0 / 202 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Brain neoplasm                                                      |                  |  |  |
| subjects affected / exposed                                         | 0 / 202 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Breast cancer                                                       |                  |  |  |
| subjects affected / exposed                                         | 0 / 202 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Haemangioma                                                         |                  |  |  |
| subjects affected / exposed                                         | 0 / 202 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Intraductal papilloma of breast                                     |                  |  |  |
| subjects affected / exposed                                         | 0 / 202 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |



|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Intraductal proliferative breast lesion         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Invasive breast carcinoma                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Laryngeal cancer stage 0                        |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Leiomyosarcoma                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Metastases to bone                              |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Non-small cell lung cancer                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ovarian germ cell teratoma benign               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Phaeochromocytoma                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pleomorphic adenoma                             |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostate cancer                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Schwannoma                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Squamous cell carcinoma of pharynx              |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Uterine leiomyoma                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic aneurysm                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Deep vein thrombosis                            |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypertension                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypertensive crisis                             |                 |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pelvic venous thrombosis                             |                 |  |  |
| subjects affected / exposed                          | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Polyarteritis nodosa                                 |                 |  |  |
| subjects affected / exposed                          | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pregnancy, puerperium and perinatal conditions       |                 |  |  |
| Abortion spontaneous                                 |                 |  |  |
| subjects affected / exposed                          | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Impaired healing                                     |                 |  |  |
| subjects affected / exposed                          | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Non-cardiac chest pain                               |                 |  |  |
| subjects affected / exposed                          | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Peripheral swelling                                  |                 |  |  |
| subjects affected / exposed                          | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia                                              |                 |  |  |
| subjects affected / exposed                          | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Reproductive system and breast disorders        |                 |  |  |
| Adenomyosis                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Adnexa uteri cyst                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endometriosis                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Menorrhagia                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metrorrhagia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pelvic adhesions                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Uterine haemorrhage                             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Haemothorax                                     |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary alveolar haemorrhage                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Cervical vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Comminuted fracture                             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eyelid injury                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Face injury                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Facial bones fracture                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fall                                            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femur fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fibula fracture                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Head injury                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Meniscus injury                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Multiple injuries                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pelvic fracture                                 |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Periprosthetic osteolysis                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rib fracture                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin abrasion                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skull fracture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sternal fracture                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subarachnoid haemorrhage                        |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thoracic vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tibia fracture                                  |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Toxicity to various agents                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Traumatic liver injury                          |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ulna fracture                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wound dehiscence                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina unstable                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Arrhythmia                                      |                 |  |  |



|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrial fibrillation                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrioventricular block second degree            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure congestive                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Coronary artery disease                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Coronary artery insufficiency                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Myocardial infarction                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Myocarditis                                     |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Palpitations                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinus node dysfunction                          |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ventricular tachycardia                         |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Cerebral haemorrhage                            |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral infarction                             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Encephalopathy                                  |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hemiplegia                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intracranial venous sinus thrombosis            |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Presyncope                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope                                         |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombotic stroke                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Haemolytic anaemia                              |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Leukocytosis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Normocytic anaemia                              |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| Vertigo positional                              |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |
| Ocular myasthenia                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal adhesions                             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aphthous ulcer                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Colitis                                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Colitis ischaemic                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Colitis ulcerative                              |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Crohn's disease                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diarrhoea haemorrhagic                          |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dysphagia                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Enteritis                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femoral hernia                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastric haemorrhage                             |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhoids                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus                                           |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inguinal hernia                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Large intestine polyp                           |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mouth ulceration                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Obstructive pancreatitis                        |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Odynophagia                                     |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oesophagitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal haemorrhage                              |                 |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Umbilical hernia                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Biliary colic                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis acute                             |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Chronic hepatitis                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Drug-induced liver injury                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Erythema nodosum                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rosacea                                         |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nephrolithiasis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ureterolithiasis                                |                 |  |  |



|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocrine disorders                             |                 |  |  |
| Basedow's disease                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Goitre                                          |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Arthritis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Foot deformity                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc degeneration                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Intervertebral disc protrusion                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Limb asymmetry                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lumbar spinal stenosis                          |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Osteoarthritis                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Osteochondrosis                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pain in extremity                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Psoriatic arthropathy                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rotator cuff syndrome                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Scoliosis                                       |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Synovitis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Abdominal sepsis                                |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abscess limb                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendiceal abscess                             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dengue fever                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea infectious                            |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticulitis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Erysipelas                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Escherichia sepsis                              |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Escherichia urinary tract infection             |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral discitis                         |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Klebsiella sepsis                               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung abscess                                    |                 |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Necrotising fasciitis                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oesophageal candidiasis                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Post procedural infection                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Prostatitis Escherichia coli                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rash pustular                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Salpingo-oophoritis                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis                                          |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinusitis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 202 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Streptococcal infection                         |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tonsillitis                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Typhoid fever                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection bacterial               |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urosepsis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Viral infection                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wound infection staphylococcal                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hyperglycaemia                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 202 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Any AIN457 150 mg  | Any AIN457 75 mg   | Any AIN457 300 mg |
|-------------------------------------------------------|--------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                   |
| subjects affected / exposed                           | 264 / 473 (55.81%) | 197 / 292 (67.47%) | 47 / 165 (28.48%) |
| Vascular disorders                                    |                    |                    |                   |
| Hypertension                                          |                    |                    |                   |
| subjects affected / exposed                           | 33 / 473 (6.98%)   | 27 / 292 (9.25%)   | 7 / 165 (4.24%)   |
| occurrences (all)                                     | 33                 | 28                 | 9                 |
| Nervous system disorders                              |                    |                    |                   |
| Headache                                              |                    |                    |                   |
| subjects affected / exposed                           | 42 / 473 (8.88%)   | 31 / 292 (10.62%)  | 1 / 165 (0.61%)   |
| occurrences (all)                                     | 67                 | 52                 | 1                 |
| Gastrointestinal disorders                            |                    |                    |                   |
| Diarrhoea                                             |                    |                    |                   |
| subjects affected / exposed                           | 38 / 473 (8.03%)   | 23 / 292 (7.88%)   | 1 / 165 (0.61%)   |
| occurrences (all)                                     | 56                 | 36                 | 1                 |
| Nausea                                                |                    |                    |                   |
| subjects affected / exposed                           | 14 / 473 (2.96%)   | 17 / 292 (5.82%)   | 3 / 165 (1.82%)   |
| occurrences (all)                                     | 16                 | 20                 | 3                 |
| Vomiting                                              |                    |                    |                   |
| subjects affected / exposed                           | 8 / 473 (1.69%)    | 15 / 292 (5.14%)   | 0 / 165 (0.00%)   |
| occurrences (all)                                     | 11                 | 19                 | 0                 |
| Respiratory, thoracic and mediastinal disorders       |                    |                    |                   |
| Cough                                                 |                    |                    |                   |
| subjects affected / exposed                           | 30 / 473 (6.34%)   | 21 / 292 (7.19%)   | 3 / 165 (1.82%)   |
| occurrences (all)                                     | 44                 | 24                 | 4                 |
| Oropharyngeal pain                                    |                    |                    |                   |
| subjects affected / exposed                           | 19 / 473 (4.02%)   | 20 / 292 (6.85%)   | 1 / 165 (0.61%)   |
| occurrences (all)                                     | 27                 | 28                 | 1                 |
| Skin and subcutaneous tissue disorders                |                    |                    |                   |
| Psoriasis                                             |                    |                    |                   |
| subjects affected / exposed                           | 23 / 473 (4.86%)   | 23 / 292 (7.88%)   | 2 / 165 (1.21%)   |
| occurrences (all)                                     | 24                 | 24                 | 2                 |
| Musculoskeletal and connective tissue disorders       |                    |                    |                   |
| Arthralgia                                            |                    |                    |                   |
| subjects affected / exposed                           | 30 / 473 (6.34%)   | 24 / 292 (8.22%)   | 3 / 165 (1.82%)   |
| occurrences (all)                                     | 41                 | 38                 | 4                 |
| Back pain                                             |                    |                    |                   |



|                                                                                       |                           |                          |                        |
|---------------------------------------------------------------------------------------|---------------------------|--------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 33 / 473 (6.98%)<br>40    | 30 / 292 (10.27%)<br>39  | 3 / 165 (1.82%)<br>3   |
| Psoriatic arthropathy<br>subjects affected / exposed<br>occurrences (all)             | 27 / 473 (5.71%)<br>32    | 23 / 292 (7.88%)<br>26   | 2 / 165 (1.21%)<br>2   |
| <b>Infections and infestations</b>                                                    |                           |                          |                        |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 35 / 473 (7.40%)<br>53    | 24 / 292 (8.22%)<br>29   | 9 / 165 (5.45%)<br>10  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 30 / 473 (6.34%)<br>46    | 10 / 292 (3.42%)<br>15   | 2 / 165 (1.21%)<br>2   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 101 / 473 (21.35%)<br>220 | 70 / 292 (23.97%)<br>138 | 14 / 165 (8.48%)<br>14 |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 22 / 473 (4.65%)<br>34    | 15 / 292 (5.14%)<br>21   | 0 / 165 (0.00%)<br>0   |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 26 / 473 (5.50%)<br>34    | 17 / 292 (5.82%)<br>29   | 3 / 165 (1.82%)<br>4   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 91 / 473 (19.24%)<br>153  | 62 / 292 (21.23%)<br>98  | 10 / 165 (6.06%)<br>17 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 27 / 473 (5.71%)<br>40    | 21 / 292 (7.19%)<br>27   | 2 / 165 (1.21%)<br>2   |

|                                                                                        |                      |  |  |
|----------------------------------------------------------------------------------------|----------------------|--|--|
| <b>Non-serious adverse events</b>                                                      | Placebo              |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 63 / 202 (31.19%)    |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all) | 5 / 202 (2.48%)<br>6 |  |  |
| Nervous system disorders                                                               |                      |  |  |

|                                                                                                                                                                                                                                                                         |                                                                              |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                            | 7 / 202 (3.47%)<br>8                                                         |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all)                                       | 6 / 202 (2.97%)<br>7<br><br>2 / 202 (0.99%)<br>2<br><br>1 / 202 (0.50%)<br>1 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                                                              | 6 / 202 (2.97%)<br>9<br><br>4 / 202 (1.98%)<br>5                             |  |  |
| Skin and subcutaneous tissue disorders<br>Psoriasis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                 | 1 / 202 (0.50%)<br>1                                                         |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Psoriatic arthropathy<br>subjects affected / exposed<br>occurrences (all) | 3 / 202 (1.49%)<br>3<br><br>2 / 202 (0.99%)<br>2<br><br>2 / 202 (0.99%)<br>2 |  |  |
| Infections and infestations                                                                                                                                                                                                                                             |                                                                              |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| Bronchitis                        |                  |  |  |
| subjects affected / exposed       | 6 / 202 (2.97%)  |  |  |
| occurrences (all)                 | 7                |  |  |
| Gastroenteritis                   |                  |  |  |
| subjects affected / exposed       | 2 / 202 (0.99%)  |  |  |
| occurrences (all)                 | 2                |  |  |
| Nasopharyngitis                   |                  |  |  |
| subjects affected / exposed       | 11 / 202 (5.45%) |  |  |
| occurrences (all)                 | 12               |  |  |
| Pharyngitis                       |                  |  |  |
| subjects affected / exposed       | 0 / 202 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Sinusitis                         |                  |  |  |
| subjects affected / exposed       | 4 / 202 (1.98%)  |  |  |
| occurrences (all)                 | 4                |  |  |
| Upper respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 12 / 202 (5.94%) |  |  |
| occurrences (all)                 | 13               |  |  |
| Urinary tract infection           |                  |  |  |
| subjects affected / exposed       | 2 / 202 (0.99%)  |  |  |
| occurrences (all)                 | 2                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

|                                                |
|------------------------------------------------|
| Observed data is reported for outcome measures |
|------------------------------------------------|

|                                                                          |
|--------------------------------------------------------------------------|
| The non-fatal adverse events are reported under "Serious Adverse Events" |
|--------------------------------------------------------------------------|

Notes: