

**Clinical trial results:****A 24-week, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Phase 2 Study of Different Doses of VX-509 in Adult Subjects With Active Rheumatoid Arthritis on Stable Methotrexate Therapy with 104-Week Open-Label Extension****Summary**

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2011-004419-22    |
| Trial protocol           | DE CZ HU EE SK BG |
| Global end of trial date | 31 July 2014      |

**Results information**

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 28 June 2016   |
| First version publication date | 07 August 2015 |

**Trial information****Trial identification**

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | VX11-509-102 |
|-----------------------|--------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01590459 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Vertex Pharmaceuticals Incorporated  |
| Sponsor organisation address | 50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862                       |
| Public contact               | Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com |
| Scientific contact           | Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.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                       | 18 September 2014 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 31 July 2014      |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of multiple doses of VX-509 when administered for 12 weeks in subjects with active RA on stable MTX therapy. To evaluate the safety and tolerability of multiple doses of VX-509 when administered for 12 weeks in subjects with active RA on stable MTX therapy.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy:

Subjects had been receiving MTX coadministered with folic or folinic acid (at least 5 mg/week) for at least 12 weeks before screening, and had been receiving MTX at a stable dose between 10 mg and 25 mg, orally or subcutaneously administered, per week for at least 8 consecutive weeks.

Evidence for comparator:

There was no active comparator.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 May 2012      |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 2 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 15          |
| Country: Number of subjects enrolled | Bulgaria: 40           |
| Country: Number of subjects enrolled | Czech Republic: 29     |
| Country: Number of subjects enrolled | Estonia: 16            |
| Country: Number of subjects enrolled | Germany: 14            |
| Country: Number of subjects enrolled | Hungary: 24            |
| Country: Number of subjects enrolled | Mexico: 41             |
| Country: Number of subjects enrolled | Poland: 39             |
| Country: Number of subjects enrolled | Romania: 3             |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | Serbia: 14             |
| Country: Number of subjects enrolled | Slovakia: 1            |
| Country: Number of subjects enrolled | Ukraine: 18            |
| Country: Number of subjects enrolled | United States: 83      |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 358 |
| EEA total number of subjects       | 166 |

Notes:

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**Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 295 |
| From 65 to 84 years                       | 63  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 359 subjects were enrolled, of which 358 subjects received study drug. Subjects with less than a 20% reduction from baseline in tender joints, swollen joints, and subject-assessed pain at Week 8 or later were eligible to enroll in Escape arm and received 150 mg VX-509 qd or 200 mg VX-509 qd.

### Period 1

|                              |                          |
|------------------------------|--------------------------|
| Period 1 title               | 24 Week Treatment Period |
| Is this the baseline period? | Yes                      |
| Allocation method            | Randomised - controlled  |
| Blinding used                | Double blind             |
| Roles blinded                | Subject, Investigator    |

### Arms

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

Arm description:

VX-509-matched placebo up to 24 weeks.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

VX-509-matched placebo up to 24 weeks.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | VX-509 100 mg qd |
|------------------|------------------|

Arm description:

VX-509 100 milligram (mg) once daily (qd) up to 24 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | VX-509       |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

VX-509 100 mg qd up to 24 weeks.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | VX- 509 150 mg qd |
|------------------|-------------------|

Arm description:

VX-509 150 mg qd up to 24 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | VX-509       |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:  
 VX-509 150 mg qd up to 24 weeks.

|  |                  |
|--|------------------|
| <b>Arm title</b>                                     | VX-509 200 mg qd |
| Arm description:<br>VX-509 200 mg qd up to 24 weeks. |                  |
| Arm type   | Experimental     |
| Investigational medicinal product name               | VX-509           |
| Investigational medicinal product code               |                  |
| Other name   |                  |
| Pharmaceutical forms                                 | Tablet           |
| Routes of administration                             | Oral use         |

Dosage and administration details:  
 VX-509 200 mg qd up to 24 weeks.

|   |                   |
|---|-------------------|
| <b>Arm title</b>  | VX-509 100 mg bid |
| Arm description:<br>VX-509 100 mg twice daily (bid) for up to 24 weeks. |                   |
| Arm type  | Experimental      |
| Investigational medicinal product name                                  | VX-509            |
| Investigational medicinal product code                                  |                   |
| Other name  |                   |
| Pharmaceutical forms  | Tablet            |
| Routes of administration  | Oral use          |

Dosage and administration details:  
 VX-509 100 mg bid up to 24 weeks.

| <b>Number of subjects in period 1</b>           | Placebo | VX-509 100 mg qd | VX- 509 150 mg qd |
|---|---------|------------------|-------------------|
| Started   | 71      | 71               | 72                |
| Completed                                       | 58      | 57               | 60                |
| Not completed                                   | 13      | 14               | 12                |
| Physician decision                              | 1       | 2                | -                 |
| Death   | -       | -                | -                 |
| Did not meet eligibility criteria               | 1       | 1                | -                 |
| Adverse event                                   | 6       | 6                | 7                 |
| Noncompliance with study drug                   | -       | 1                | -                 |
| Unspecified                                     | 1       | 1                | -                 |
| Lost to follow-up                               | 2       | 1                | -                 |
| Refused further dosing for reason other than AE | 2       | 2                | 5                 |

| <b>Number of subjects in period 1</b> | VX-509 200 mg qd | VX-509 100 mg bid |
|---------------------------------------|------------------|-------------------|
| Started                               | 72               | 72                |

|   |    |    |
|---|----|----|
| Completed                                       | 59 | 61 |
| Not completed                                   | 13 | 11 |
| Physician decision                              | -  | -  |
| Death   | -  | 1  |
| Did not meet eligibility criteria               | 2  | -  |
| Adverse event                                   | 9  | 3  |
| Noncompliance with study drug                   | -  | -  |
| Unspecified                                     | -  | -  |
| Lost to follow-up                               | -  | 1  |
| Refused further dosing for reason other than AE | 2  | 6  |

## Period 2

|                              |                            |
|------------------------------|----------------------------|
| Period 2 title               | Open Label Extension (OLE) |
| Is this the baseline period? | No                         |
| Allocation method            | Not applicable             |
| Blinding used                | Not blinded                |

## Arms

|                              |                        |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes                    |
| <b>Arm title</b>             | VX-509 150 mg qd - OLE |

Arm description:

VX-509 150 mg qd up to 104 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | VX-509       |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

VX-509 150 mg qd up to 104 weeks.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | VX-509 200 mg qd - OLE |
|------------------|------------------------|

Arm description:

VX-509 200 mg qd up to 104 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | VX-509       |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

VX-509 200 mg qd up to 104 weeks.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | VX-509 150 mg qd - OLE | VX-509 200 mg qd - OLE |
|---|------------------------|------------------------|
| Started   | 47                     | 218                    |
| Completed   | 0                      | 0                      |
| Not completed                                       | 47                     | 218                    |
| Required prohibited medication                      | -                      | 1                      |
| Death   | -                      | 1                      |
| Did not meet eligibility criteria                   | -                      | 8                      |
| Adverse event                                       | 2                      | 8                      |
| Study terminated by sponsor                         | 42                     | 188                    |
| Unspecified   | -                      | 5                      |
| Lost to follow-up                                   | 1                      | 1                      |
| Refused further dosing for reason other than AE     | 2                      | 6                      |

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only subjects who completed 24 weeks of treatment in the Treatment Period and who had at least an ACR20-CRP response were eligible for OLE.

## Baseline characteristics

### Reporting groups

|   |                   |
|---|-------------------|
| Reporting group title   | Placebo           |
| Reporting group description:<br>VX-509-matched placebo up to 24 weeks.                    |                   |
| Reporting group title   | VX-509 100 mg qd  |
| Reporting group description:<br>VX-509 100 milligram (mg) once daily (qd) up to 24 weeks. |                   |
| Reporting group title   | VX- 509 150 mg qd |
| Reporting group description:<br>VX-509 150 mg qd up to 24 weeks.                          |                   |
| Reporting group title   | VX-509 200 mg qd  |
| Reporting group description:<br>VX-509 200 mg qd up to 24 weeks.                          |                   |
| Reporting group title   | VX-509 100 mg bid |
| Reporting group description:<br>VX-509 100 mg twice daily (bid) for up to 24 weeks.       |                   |

| Reporting group values             | Placebo | VX-509 100 mg qd | VX- 509 150 mg qd |
|------------------------------------|---------|------------------|-------------------|
| Number of subjects                 | 71      | 71               | 72                |
| Age categorical<br>Units: Subjects |         |                  |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 52.7<br>± 13.16 | 53.5<br>± 11.33 | 50.1<br>± 11.81 |
| Gender categorical<br>Units: Subjects                                   |                 |                 |                 |
| Female  | 62              | 51              | 58              |
| Male  | 9               | 20              | 14              |

| Reporting group values             | VX-509 200 mg qd | VX-509 100 mg bid | Total |
|------------------------------------|------------------|-------------------|-------|
| Number of subjects                 | 72               | 72                | 358   |
| Age categorical<br>Units: Subjects |                  |                   |       |

|   |                 |                 |     |
|---|-----------------|-----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 53.2<br>± 13.21 | 55.7<br>± 12.23 | -   |
| Gender categorical<br>Units: Subjects                                   |                 |                 |     |
| Female  | 56              | 62              | 289 |
| Male  | 16              | 10              | 69  |

## End points

### End points reporting groups

|                                   |   |
|-----------------------------------|---|
| Reporting group title             | Placebo   |
| Reporting group description:      | VX-509-matched placebo up to 24 weeks.  |
| Reporting group title             | VX-509 100 mg qd  |
| Reporting group description:      | VX-509 100 milligram (mg) once daily (qd) up to 24 weeks.   |
| Reporting group title             | VX- 509 150 mg qd   |
| Reporting group description:      | VX-509 150 mg qd up to 24 weeks.  |
| Reporting group title             | VX-509 200 mg qd  |
| Reporting group description:      | VX-509 200 mg qd up to 24 weeks.  |
| Reporting group title             | VX-509 100 mg bid   |
| Reporting group description:      | VX-509 100 mg twice daily (bid) for up to 24 weeks.   |
| Reporting group title             | VX-509 150 mg qd - OLE  |
| Reporting group description:      | VX-509 150 mg qd up to 104 weeks.   |
| Reporting group title             | VX-509 200 mg qd - OLE  |
| Reporting group description:      | VX-509 200 mg qd up to 104 weeks.   |
| Subject analysis set title        | VX-509 150 mg qd - Treatment Period, After Escape   |
| Subject analysis set type         | Safety analysis   |
| Subject analysis set description: | Subjects with less than a 20% reduction from baseline in tender joints, swollen joints, and subject-assessed pain at Week 8 or later enrolled in Escape arm and received VX-509 150 mg qd.      |
| Subject analysis set title        | VX-509 200 mg qd - Treatment Period, After Escape   |
| Subject analysis set type         | Safety analysis   |
| Subject analysis set description: | Subjects with less than a 20% reduction from baseline in tender joints, swollen joints, and subject-assessed pain at Week 8 or later were enrolled in Escape arm and received VX-509 200 mg qd. |

### **Primary: Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) C-Reactive Protein (ACR20-CRP) Response at Week 12**

|                        |   |
|------------------------|---|
| End point title        | Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) C-Reactive Protein (ACR20-CRP) Response at Week 12  |
| End point description: | ACR20-CRP response: greater than equal to ( $\geq$ ) 20% improvement in tender joints count (TJC); $\geq$ 20% improvement in swollen joints count (SJC); and $\geq$ 20% improvement in at least 3 of 5 remaining ACR core measures: subject assessment of pain (assessed on 0-100 mm VAS, higher score = more pain); subject global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); physician global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and CRP levels. Full analysis set included all randomized subjects who received at least 1 dose of study drug. |
| End point type         | Primary   |
| End point timeframe:   | Week 12   |

| <b>End point values</b>       | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type            | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed   | 71              | 71               | 72                | 72               |
| Units: percentage of subjects |                 |                  |                   |                  |
| number (not applicable)       | 18.3            | 46.5             | 66.7              | 56.9             |

| <b>End point values</b>       | VX-509 100 mg bid |  |  |  |
|-------------------------------|-------------------|--|--|--|
| Subject group type            | Reporting group   |  |  |  |
| Number of subjects analysed   | 72                |  |  |  |
| Units: percentage of subjects |                   |  |  |  |
| number (not applicable)       | 68.1              |  |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
| Comparison groups                       | VX-509 100 mg qd v Placebo |
| Number of subjects included in analysis | 142                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.0002                   |
| Method                                  | Wald asymptotic test       |
| Parameter estimate                      | Proportion difference      |
| Point estimate                          | 28.2                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 13.5                       |
| upper limit                             | 42.8                       |

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | VX- 509 150 mg qd v Placebo |
| Number of subjects included in analysis | 143                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | < 0.0001                    |
| Method                                  | Wald asymptotic test        |
| Parameter estimate                      | Proportion difference       |
| Point estimate                          | 48.4                        |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 34.2    |
| upper limit         | 62.5    |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo v VX-509 200 mg qd |
| Number of subjects included in analysis | 143                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.0001                   |
| Method                                  | Wald asymptotic test       |
| Parameter estimate                      | Proportion difference      |
| Point estimate                          | 38.6                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 24.1                       |
| upper limit                             | 53.2                       |

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 4      |
| Comparison groups                       | VX-509 100 mg bid v Placebo |
| Number of subjects included in analysis | 143                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | < 0.0001                    |
| Method                                  | Wald asymptotic test        |
| Parameter estimate                      | Proportion difference       |
| Point estimate                          | 49.7                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 35.7                        |
| upper limit                             | 63.8                        |

**Primary: Change From Baseline in Disease Activity Score Using 28-Joint Count and C-Reactive Protein (4 Variables) (DAS28-4 [CRP]) at Week 12**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Disease Activity Score Using 28-Joint Count and C-Reactive Protein (4 Variables) (DAS28-4 [CRP]) at Week 12 |
|-----------------|---|

End point description:

DAS28-4 (CRP) was calculated from SJC and TJC using the 28 joints count, CRP milligram per liter [mg/L] and subject general health visual analogue scale score. A score of less than (<2.6) implied remission, <=3.2 implied low disease activity. Full analysis set included all randomized subjects who

received at least 1 dose of study drug.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Baseline and Week 12 |         |

| <b>End point values</b>             | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type                  | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed         | 71              | 70               | 70                | 69               |
| Units: units on scale               |                 |                  |                   |                  |
| least squares mean (standard error) | -0.76 (± 0.157) | -2.05 (± 0.146)  | -2.22 (± 0.14)    | -2.48 (± 0.146)  |

| <b>End point values</b>             | VX-509 100 mg bid |  |  |  |
|-------------------------------------|-------------------|--|--|--|
| Subject group type                  | Reporting group   |  |  |  |
| Number of subjects analysed         | 71                |  |  |  |
| Units: units on scale               |                   |  |  |  |
| least squares mean (standard error) | -2.39 (± 0.142)   |  |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
|---|----------------------------|
| Comparison groups                       | VX-509 100 mg qd v Placebo |
| Number of subjects included in analysis | 141                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.0001                   |
| Method                                  | Mixed effect model         |
| Parameter estimate                      | Treatment difference       |
| Point estimate                          | -1.28                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.68                      |
| upper limit                             | -0.88                      |

| <b>Statistical analysis title</b> | Statistical Analysis 2      |
|-----------------------------------|-----------------------------|
| Comparison groups                 | VX- 509 150 mg qd v Placebo |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 141                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | < 0.0001             |
| Method                                  | Mixed effect model   |
| Parameter estimate                      | Treatment difference |
| Point estimate                          | -1.46                |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -1.85                |
| upper limit                             | -1.06                |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | VX-509 200 mg qd v Placebo |
| Number of subjects included in analysis | 140                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.0001                   |
| Method                                  | Mixed effect model         |
| Parameter estimate                      | Treatment difference       |
| Point estimate                          | -1.71                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.11                      |
| upper limit                             | -1.32                      |

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 4      |
| Comparison groups                       | VX-509 100 mg bid v Placebo |
| Number of subjects included in analysis | 142                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | < 0.0001                    |
| Method                                  | Mixed effect model          |
| Parameter estimate                      | Treatment difference        |
| Point estimate                          | -1.62                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -2.01                       |
| upper limit                             | -1.23                       |

### **Primary: Safety and Tolerability as Assessed by Adverse Events (AEs) Through Week**

|                 |  |
|-----------------|--|
| End point title | Safety and Tolerability as Assessed by Adverse Events (AEs) Through Week 24 <sup>[1]</sup> |
|-----------------|--|

End point description:

AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed. AE included serious as well as non-serious AEs. Serious adverse event (SAE) (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. Safety set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Through Week 24

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: Statistical analysis was not planned for safety endpoint.

| End point values            | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-----------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type          | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed | 71              | 71               | 72                | 72               |
| Units: number of subjects   |                 |                  |                   |                  |
| number (not applicable)     |                 |                  |                   |                  |
| Subjects with AEs           | 30              | 37               | 44                | 49               |
| Subjects with SAEs          | 4               | 3                | 6                 | 5                |

| End point values            | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|-----------------------------|-------------------|---|---|--|
| Subject group type          | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed | 72                | 29  | 64  |  |
| Units: number of subjects   |                   |   |   |  |
| number (not applicable)     |                   |   |   |  |
| Subjects with AEs           | 42                | 11  | 36  |  |
| Subjects with SAEs          | 7                 | 1   | 5   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving ACR-CRP Responses

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Achieving ACR-CRP Responses |
|-----------------|--|

End point description:

ACR20-CRP at Week 24 and ACR50/70-CRP at Week 12 and 24 are reported. ACR20-CRP is defined in

first primary endpoint. ACR50/70-CRP response:  $\geq 50\%/70\%$  improvement in TJC;  $\geq 50\%/70\%$  improvement in SJC; and  $\geq 50\%/70\%$  improvement in at least 3 of 5 remaining ACR core measures: subject assessment of pain (assessed on 0-100 mm VAS, higher score = more pain); subject global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); physician global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); self-assessed disability (disability index of the HAQ); and CRP levels. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12 and 24       |           |

| End point values              | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type            | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed   | 71              | 71               | 72                | 72               |
| Units: percentage of subjects |                 |                  |                   |                  |
| number (not applicable)       |                 |                  |                   |                  |
| Week 24: ACR20 CRP            | 16.9            | 60.6             | 61.1              | 61.1             |
| Week 12: ACR50 CRP            | 7               | 22.5             | 38.9              | 34.7             |
| Week 12: ACR70 CRP            | 2.8             | 9.9              | 11.1              | 9.7              |
| Week 24: ACR50 CRP            | 7               | 38               | 38.9              | 40.3             |
| Week 24: ACR70 CRP            | 2.8             | 16.9             | 18.1              | 15.3             |

| End point values              | VX-509 100 mg bid |  |  |  |
|-------------------------------|-------------------|--|--|--|
| Subject group type            | Reporting group   |  |  |  |
| Number of subjects analysed   | 72                |  |  |  |
| Units: percentage of subjects |                   |  |  |  |
| number (not applicable)       |                   |  |  |  |
| Week 24: ACR20 CRP            | 62.5              |  |  |  |
| Week 12: ACR50 CRP            | 38.9              |  |  |  |
| Week 12: ACR70 CRP            | 22.2              |  |  |  |
| Week 24: ACR50 CRP            | 47.2              |  |  |  |
| Week 24: ACR70 CRP            | 25                |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects who Achieved a Moderate or Good Response with European League Against Rheumatism (EULAR) Response at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects who Achieved a Moderate or Good Response with European League Against Rheumatism (EULAR) Response at Week 12 and 24 |
|-----------------|--|

End point description:

DAS28-4 (CRP) EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached.

Good responders: change from baseline >1.2 with DAS28-4 (CRP) =< 3.2; moderate responders: change from baseline >1.2 with DAS28-4 (CRP) >3.2 or change from baseline >0.6 to =<1.2 with DAS28-4 (CRP) =<5.1; non-responders: change from baseline =< 0.6 or change from baseline >0.6 and =<1.2 with DAS28-4 CPR >5.1. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12 and 24       |           |

| <b>End point values</b>       | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type            | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed   | 71              | 71               | 72                | 72               |
| Units: percentage of subjects |                 |                  |                   |                  |
| number (not applicable)       |                 |                  |                   |                  |
| Week 12                       | 25.4            | 57.7             | 69.4              | 65.3             |
| Week 24                       | 19.7            | 56.3             | 62.5              | 61.1             |

| <b>End point values</b>       | VX-509 100 mg bid |  |  |  |
|-------------------------------|-------------------|--|--|--|
| Subject group type            | Reporting group   |  |  |  |
| Number of subjects analysed   | 72                |  |  |  |
| Units: percentage of subjects |                   |  |  |  |
| number (not applicable)       |                   |  |  |  |
| Week 12                       | 68.1              |  |  |  |
| Week 24                       | 61.1              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with DAS28-4 (CRP) Remission at Week 12 and 24

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with DAS28-4 (CRP) Remission at Week 12 and 24 |
|-----------------|---|

End point description:

DAS28-4 (CRP) is defined in second primary endpoint. DAS28-4 (CRP) score <2.6 was considered remission. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12 and 24       |           |

| <b>End point values</b>       | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type            | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed   | 71              | 71               | 72                | 72               |
| Units: percentage of subjects |                 |                  |                   |                  |
| number (not applicable)       |                 |                  |                   |                  |
| Week 12                       | 2.8             | 16.9             | 29.2              | 22.2             |
| Week 24                       | 5.6             | 21.1             | 29.2              | 27.8             |

| <b>End point values</b>       | VX-509 100 mg bid |  |  |  |
|-------------------------------|-------------------|--|--|--|
| Subject group type            | Reporting group   |  |  |  |
| Number of subjects analysed   | 72                |  |  |  |
| Units: percentage of subjects |                   |  |  |  |
| number (not applicable)       |                   |  |  |  |
| Week 12                       | 30.6              |  |  |  |
| Week 24                       | 31.9              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in DAS28-4 (CRP) at Week 24

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in DAS28-4 (CRP) at Week 24  |
| End point description: | DAS28-4 (CRP) is defined in second primary endpoint. Full analysis set included all randomized subjects who received at least 1 dose of study drug. |
| End point type         | Secondary   |
| End point timeframe:   | Baseline, Week 24   |

| <b>End point values</b>             | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type                  | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed         | 71              | 70               | 70                | 69               |
| Units: units on scale               |                 |                  |                   |                  |
| least squares mean (standard error) | -1.51 (± 0.215) | -2.35 (± 0.158)  | -2.35 (± 0.148)   | -2.68 (± 0.156)  |

| <b>End point values</b>     | VX-509 100 mg bid |  |  |  |
|-----------------------------|-------------------|--|--|--|
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 71                |  |  |  |

|                                     |                 |  |  |  |
|-------------------------------------|-----------------|--|--|--|
| Units: units on scale               |                 |  |  |  |
| least squares mean (standard error) | -2.86 (± 0.154) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects who Achieved Remission as Defined by the ACR/EULAR Criteria

|   |  |
|---|--|
| End point title   | Percentage of Subjects who Achieved Remission as Defined by the ACR/EULAR Criteria |
| End point description:  |  |
| Subject was considered to be in remission when either scores on the tender joint count, swollen joint count, CRP (in mg/dL), and subject global assessment (0 to 10 scale) were all ≤1; or score on the Simplified Disease Activity Index (SDAI) was ≤3.3. Full analysis set included all randomized subjects who received at least 1 dose of study drug. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Week 12 and 24  |  |

| End point values              | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type            | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed   | 71              | 71               | 72                | 72               |
| Units: percentage of subjects |                 |                  |                   |                  |
| number (not applicable)       |                 |                  |                   |                  |
| Week 12                       | 0               | 5.6              | 5.6               | 6.9              |
| Week 24                       | 0               | 9.9              | 11.1              | 6.9              |

| End point values              | VX-509 100 mg bid |  |  |  |
|-------------------------------|-------------------|--|--|--|
| Subject group type            | Reporting group   |  |  |  |
| Number of subjects analysed   | 72                |  |  |  |
| Units: percentage of subjects |                   |  |  |  |
| number (not applicable)       |                   |  |  |  |
| Week 12                       | 6.9               |  |  |  |
| Week 24                       | 15.3              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) at Week 12 and Week 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) at Week 12 and Week 24 |
|-----------------|--|

End point description:

The HAQ-DI is a self-completed subject questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. Domain score = total score of individual questions divided by total number of questions. HAQ-DI total score = total of domain scores divided by number of domains, range: 0 (best) to 3 (worst). Full analysis set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Week 12 and 24

| End point values                    | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|-------------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type                  | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed         | 71              | 71               | 72                | 72               |
| Units: units on scale               |                 |                  |                   |                  |
| least squares mean (standard error) |                 |                  |                   |                  |
| Week 12                             | -0.28 (± 0.071) | -0.49 (± 0.068)  | -0.58 (± 0.065)   | -0.63 (± 0.068)  |
| Week 24                             | -0.6 (± 0.09)   | -0.62 (± 0.07)   | -0.65 (± 0.067)   | -0.79 (± 0.069)  |

| End point values                    | VX-509 100 mg bid |  |  |  |
|-------------------------------------|-------------------|--|--|--|
| Subject group type                  | Reporting group   |  |  |  |
| Number of subjects analysed         | 72                |  |  |  |
| Units: units on scale               |                   |  |  |  |
| least squares mean (standard error) |                   |  |  |  |
| Week 12                             | -0.62 (± 0.066)   |  |  |  |
| Week 24                             | -0.75 (± 0.068)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Subject Global Assessment of Disease Activity at Week 12 and 24

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Subject Global Assessment of Disease Activity at Week 12 and 24 |
|-----------------|---|

End point description:

Subject assessed overall arthritis activity on an 11-point scale ranging from 0 (none) to 10 (extreme).

Full analysis set included all randomized subjects who received at least 1 dose of study drug.

|                               |           |
|-------------------------------|-----------|
| End point type                | Secondary |
| End point timeframe:          |           |
| Baseline, Week 12 and Week 24 |           |

| <b>End point values</b>                 | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|---|-----------------|------------------|-------------------|------------------|
| Subject group type                      | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed             | 71              | 71               | 72                | 72               |
| Units: units on scale                   |                 |                  |                   |                  |
| arithmetic mean (standard deviation)    |                 |                  |                   |                  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | -1.3 (± 2.31)   | -2.6 (± 2.62)    | -2.8 (± 2.13)     | -2.8 (± 2.37)    |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | -1.9 (± 3.2)    | -3.9 (± 2.19)    | -2.9 (± 2.46)     | -3.7 (± 2.3)     |

| <b>End point values</b>                 | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|---|-------------------|---|---|--|
| Subject group type                      | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed             | 72                | 29  | 64  |  |
| Units: units on scale                   |                   |   |   |  |
| arithmetic mean (standard deviation)    |                   |   |   |  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | -3.6 (± 2.66)     | -2.2 (± 1.8)                                      | -2.3 (± 1.88)                                     |  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | -4.5 (± 2.34)     | -3.4 (± 2.55)                                     | -3.1 (± 2.8)                                      |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Subject Assessment of Pain Visual Analog Scale (VAS) Score at Week 12 and 24

|  |  |
|--|--|
| End point title  | Change from Baseline in Subject Assessment of Pain Visual Analog Scale (VAS) Score at Week 12 and 24 |
| End point description:   |  |
| Subjects indicated the amount of pain they were experiencing using a 100 millimeter (mm) VAS. VAS range: 0 mm (no pain) to 100 mm (pain as bad as it could be). Full analysis set included all randomized subjects who received at least 1 dose of study drug. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, Week 12 and 24   |  |

| <b>End point values</b>                 | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|---|-----------------|------------------|-------------------|------------------|
| Subject group type                      | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed             | 71              | 71               | 72                | 72               |
| Units: millimeter (mm)                  |                 |                  |                   |                  |
| arithmetic mean (standard deviation)    |                 |                  |                   |                  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | -10.1 (± 22.68) | -22.4 (± 26.57)  | -24.4 (± 22.51)   | -25.5 (± 25.17)  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | -19.3 (± 32.17) | -34.8 (± 22.3)   | -25.8 (± 26.78)   | -34.8 (± 25.38)  |

| <b>End point values</b>                 | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|---|-------------------|---|---|--|
| Subject group type                      | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed             | 72                | 29  | 64  |  |
| Units: millimeter (mm)                  |                   |   |   |  |
| arithmetic mean (standard deviation)    |                   |   |   |  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | -31.6 (± 25.02)   | -22.5 (± 18.67)                                   | -22.1 (± 18.54)                                   |  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | -41.4 (± 23.09)   | -31.8 (± 24.99)                                   | -30 (± 22.04)                                     |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Subject General Health VAS Score at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Subject General Health VAS Score at Week 12 and 24 |
|-----------------|--|

End point description:

Subjects rated their health using a 100 mm VAS. VAS range: 0 mm (very well) to 100 mm (extremely bad). Full analysis set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>                 | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|---|-----------------|------------------|-------------------|------------------|
| Subject group type                      | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed             | 71              | 71               | 72                | 72               |
| Units: millimeter (mm)                  |                 |                  |                   |                  |
| arithmetic mean (standard deviation)    |                 |                  |                   |                  |
| Week 12 (n= 39, 52, 59, 52, 58, 18, 45) | -7.3 (± 24.3)   | -18.6 (± 23.69)  | -19.7 (± 24.69)   | -21.2 (± 23.3)   |
| Week 24 (n= 17, 44, 53, 47, 49, 26, 55) | -18.2 (± 33.1)  | -24.2 (± 24.2)   | -19 (± 23.89)     | -28.9 (± 23.1)   |

| <b>End point values</b>                 | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|---|-------------------|---|---|--|
| Subject group type                      | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed             | 72                | 29  | 64  |  |
| Units: millimeter (mm)                  |                   |   |   |  |
| arithmetic mean (standard deviation)    |                   |   |   |  |
| Week 12 (n= 39, 52, 59, 52, 58, 18, 45) | -23.8 (± 26.17)   | -21.6 (± 26.95)                                   | -22.6 (± 24.48)                                   |  |
| Week 24 (n= 17, 44, 53, 47, 49, 26, 55) | -35.4 (± 25.41)   | -29.3 (± 27.33)                                   | -31.8 (± 24.15)                                   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Physical Component and Mental Component of the Short Form-36 (SF-36) at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Physical Component and Mental Component of the Short Form-36 (SF-36) at Week 12 and 24 |
|-----------------|--|

End point description:

SF-36 is a standardized survey evaluating 8 aspects of functional health and wellbeing: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, mental health. These 8 aspects can also be summarized as physical and mental component scores (CS). The score for a section is an average of the individual question scores, which are scaled 0-100 (100=highest level of functioning). Change from baseline in physical (PC) and mental component (MC) norm based scores (NBS) are reported. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>                          | Placebo           | VX-509 100 mg qd  | VX- 509 150 mg qd | VX-509 200 mg qd  |
|--|-------------------|-------------------|-------------------|-------------------|
| Subject group type                               | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed                      | 71                | 71                | 72                | 72                |
| Units: units on scale                            |                   |                   |                   |                   |
| arithmetic mean (standard deviation)             |                   |                   |                   |                   |
| Week 12 - MC NBS (n= 39, 52, 59, 52, 58, 15, 42) | 2.056 (± 10.7207) | 4.525 (± 11.5951) | 5.022 (± 9.3893)  | 6.039 (± 10.8664) |
| Week 12 - PC NBS (n= 39, 51, 59, 52, 58, 15, 42) | 5.508 (± 7.7841)  | 6.116 (± 5.8375)  | 7.447 (± 7.2476)  | 8.642 (± 6.9517)  |
| Week 24 - MC NBS (n= 17, 44, 53, 47, 50, 27, 55) | 7.429 (± 12.3269) | 4.641 (± 11.3092) | 5.347 (± 10.068)  | 8.479 (± 9.9463)  |
| Week 24 - PC NBS (n= 17, 43, 53, 47, 50, 27, 55) | 10.411 (± 8.2095) | 8.12 (± 6.9881)   | 9.066 (± 8.8524)  | 11.444 (± 7.9637) |

| <b>End point values</b>                          | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|--|-------------------|---|---|--|
| Subject group type                               | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed                      | 72                | 29  | 64  |  |
| Units: units on scale                            |                   |   |   |  |
| arithmetic mean (standard deviation)             |                   |   |   |  |
| Week 12 - MC NBS (n= 39, 52, 59, 52, 58, 15, 42) | 5.886 (± 10.7011) | 1.76 (± 10.5982)                                  | 3.558 (± 10.047)                                  |  |
| Week 12 - PC NBS (n= 39, 51, 59, 52, 58, 15, 42) | 8.936 (± 8.4752)  | 5.482 (± 5.4057)                                  | 4.383 (± 5.4056)                                  |  |
| Week 24 - MC NBS (n= 17, 44, 53, 47, 50, 27, 55) | 7.705 (± 11.9373) | 4.669 (± 9.4316)                                  | 4.157 (± 8.4898)                                  |  |
| Week 24 - PC NBS (n= 17, 43, 53, 47, 50, 27, 55) | 11.168 (± 7.3012) | 8.961 (± 8.5279)                                  | 6.977 (± 7.4528)                                  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) Score at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) Score at Week 12 and 24 |
|-----------------|--|

End point description:

The RAQoL questionnaire is a 30-item self-administered measure that was specifically designed to assess the health-related quality of life of people with RA. Each item is in the form a simple statement to which subjects respond "Yes" or "No." "Yes" scores 1 and "No" scores 0. The overall score is the sum of the individual item scores, ranging from 0 to 30, with a lower score indicating better quality of life. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>                 | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|---|-----------------|------------------|-------------------|------------------|
| Subject group type                      | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed             | 71              | 71               | 72                | 72               |
| Units: units on scale                   |                 |                  |                   |                  |
| arithmetic mean (standard deviation)    |                 |                  |                   |                  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | -3.05 (± 7.247) | -5.37 (± 8.049)  | -5.11 (± 5.272)   | -6.67 (± 6.597)  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | -5.35 (± 9.219) | -7.34 (± 9.514)  | -6.16 (± 6.404)   | -8.76 (± 7.053)  |

| <b>End point values</b>                 | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|---|-------------------|---|---|--|
| Subject group type                      | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed             | 72                | 29  | 64  |  |
| Units: units on scale                   |                   |   |   |  |
| arithmetic mean (standard deviation)    |                   |   |   |  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | -6.59 (± 7.923)   | -2.37 (± 6.066)                                   | -2.89 (± 7.101)                                   |  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | -7.98 (± 7.249)   | -4.78 (± 7.49)                                    | -4.65 (± 6.692)                                   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Subject-Assessed Duration of Morning Stiffness at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Subject-Assessed Duration of Morning Stiffness at Week 12 and 24 |
|-----------------|--|

End point description:

Morning stiffness was defined as stiffness in and around the joints, assessed by subject. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>              | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|--------------------------------------|-----------------|------------------|-------------------|------------------|
| Subject group type                   | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed          | 71              | 71               | 72                | 72               |
| Units: minutes                       |                 |                  |                   |                  |
| arithmetic mean (standard deviation) |                 |                  |                   |                  |
| Week 12 (38, 51, 59, 52, 57, 19, 44) | -37 (± 49.44)   | -64.1 (± 63.19)  | -60.4 (± 69.91)   | -61.3 (± 49.71)  |
| Week 24 (16, 43, 52, 47, 50, 27, 54) | -59.7 (± 68.03) | -71.5 (± 52.66)  | -72.3 (± 71.22)   | -67.1 (± 52.35)  |

| <b>End point values</b>              | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|--------------------------------------|-------------------|---|---|--|
| Subject group type                   | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed          | 72                | 29  | 64  |  |
| Units: minutes                       |                   |   |   |  |
| arithmetic mean (standard deviation) |                   |   |   |  |
| Week 12 (38, 51, 59, 52, 57, 19, 44) | -73 (± 63.25)     | -35.3 (± 88.65)                                   | -39.9 (± 60.21)                                   |  |
| Week 24 (16, 43, 52, 47, 50, 27, 54) | -79.1 (± 74.01)   | -72.4 (± 52.75)                                   | -67.2 (± 71.91)                                   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale Score at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale Score at Week 12 and 24 |
|-----------------|--|

End point description:

The FACIT-F is a 13-item self-administered tool that measures an individual's level of fatigue during usual daily activities over the past week. The level of fatigue is measured on a five-point Likert-type scale from 4 = not at all fatigued to 0 = very much fatigued; some questions are reverse-scored. The FACIT-Fatigue score is the sum of the individual item scores multiplied by 13 and divided by the number of items answered; the range is 0 to 52, with higher scores indicating better quality of life. Full analysis set included all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>                 | Placebo         | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|---|-----------------|------------------|-------------------|------------------|
| Subject group type                      | Reporting group | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed             | 71              | 71               | 72                | 72               |
| Units: units on scale                   |                 |                  |                   |                  |
| arithmetic mean (standard deviation)    |                 |                  |                   |                  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | 5.13 (± 10.603) | 5.76 (± 10.845)  | 6.36 (± 7.998)    | 8.49 (± 10.299)  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | 9.24 (± 12.77)  | 8.45 (± 11.487)  | 6.83 (± 9.468)    | 12.23 (± 11.309) |

| <b>End point values</b>                 | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|---|-------------------|---|---|--|
| Subject group type                      | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed             | 72                | 29  | 64  |  |
| Units: units on scale                   |                   |   |   |  |
| arithmetic mean (standard deviation)    |                   |   |   |  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | 10.39 (± 10.994)  | 3.11 (± 8.333)                                    | 3.38 (± 8.778)                                    |  |
| Week 24 (n= 17, 44, 53, 47, 50, 27, 55) | 12.69 (± 10.017)  | 7.3 (± 11.207)                                    | 6.04 (± 8.604)                                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Medical Outcomes Study-Sleep Module questionnaire (MOS-Sleep) Overall 9-Item Index Score at Week 12 and 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Medical Outcomes Study-Sleep Module questionnaire (MOS-Sleep) Overall 9-Item Index Score at Week 12 and 24 |
|-----------------|--|

End point description:

The MOS Sleep Scale is a subject-rated questionnaire consisting of 12 items that assess the key constructs of sleep; assesses sleep for the 4 weeks prior to evaluation. The MOS Overall Sleep Problems Index is a 9-item sub-scale; norm based scores (NBS) range from 0 to 100, lower scores indicate fewer sleep problems. Full analysis set included all randomized subjects who received at least 1 dose of study drug

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>              | Placebo           | VX-509 100 mg qd | VX- 509 150 mg qd | VX-509 200 mg qd |
|--------------------------------------|-------------------|------------------|-------------------|------------------|
| Subject group type                   | Reporting group   | Reporting group  | Reporting group   | Reporting group  |
| Number of subjects analysed          | 71                | 71               | 72                | 72               |
| Units: units on scale                |                   |                  |                   |                  |
| arithmetic mean (standard deviation) |                   |                  |                   |                  |
| Week 12 (39, 51, 57, 51, 55, 19, 45) | 5.541 (± 10.2069) | 6.162 (± 8.1018) | 6.107 (± 7.0598)  | 5.752 (± 8.5562) |
| Week 24 (17, 44, 50, 44, 49, 27, 55) | 9.906 (± 13.1697) | 6.953 (± 8.6609) | 7.102 (± 6.4437)  | 8.325 (± 9.4486) |

| <b>End point values</b>              | VX-509 100 mg bid | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|--------------------------------------|-------------------|---|---|--|
| Subject group type                   | Reporting group   | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed          | 72                | 29  | 64  |  |
| Units: units on scale                |                   |   |   |  |
| arithmetic mean (standard deviation) |                   |   |   |  |
| Week 12 (39, 51, 57, 51, 55, 19, 45) | 7.834 (± 7.6625)  | 2.143 (± 8.44)                                    | 5.862 (± 7.4288)                                  |  |
| Week 24 (17, 44, 50, 44, 49, 27, 55) | 7.303 (± 7.8772)  | 4.471 (± 7.3857)                                  | 5.281 (± 7.0525)                                  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the EuroQol (EQ-5D) Total Score at Week 12 and 24

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the EuroQol (EQ-5D) Total Score at Week 12 and 24 |
|-----------------|---|

End point description:

The EQ-5D is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1=no problems, 2=some problems, 3=extreme problems). The responses to the five EQ-5D dimensions were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1, with 1.00 indicating "full health" and 0 representing dead. Full analysis set included all randomized subjects who received at least 1 dose of study drug

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

End point timeframe:

Baseline, Week 12 and 24

| <b>End point values</b>                 | Placebo            | VX-509 100 mg qd   | VX- 509 150 mg qd  | VX-509 200 mg qd   |
|---|--------------------|--------------------|--------------------|--------------------|
| Subject group type                      | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed             | 71                 | 71                 | 72                 | 72                 |
| Units: units on scale                   |                    |                    |                    |                    |
| arithmetic mean (standard deviation)    |                    |                    |                    |                    |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | 0.1413 (± 0.2555)  | 0.1313 (± 0.19425) | 0.1146 (± 0.16821) | 0.1767 (± 0.19794) |
| Week 24 (n= 17, 44, 52, 47, 50, 27, 55) | 0.1875 (± 0.27244) | 0.1797 (± 0.24581) | 0.136 (± 0.18494)  | 0.2294 (± 0.20718) |

| <b>End point values</b>                 | VX-509 100 mg bid  | VX-509 150 mg qd - Treatment Period, After Escape | VX-509 200 mg qd - Treatment Period, After Escape |  |
|---|--------------------|---|---|--|
| Subject group type                      | Reporting group    | Subject analysis set                              | Subject analysis set                              |  |
| Number of subjects analysed             | 72                 | 29  | 64  |  |
| Units: units on scale                   |                    |   |   |  |
| arithmetic mean (standard deviation)    |                    |   |   |  |
| Week 12 (n= 39, 52, 59, 52, 58, 19, 45) | 0.1621 (± 0.18571) | 0.0634 (± 0.15886)                                | 0.0785 (± 0.17708)                                |  |
| Week 24 (n= 17, 44, 52, 47, 50, 27, 55) | 0.1974 (± 0.20298) | 0.1305 (± 0.19656)                                | 0.1093 (± 0.17024)                                |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to 28 days after last dose of study drug

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Placebo - Before Escape |
|-----------------------|-------------------------|

Reporting group description:

VX-509-matched placebo qd up to 24 weeks.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | VX-509 100 mg qd - Before Escape |
|-----------------------|----------------------------------|

Reporting group description:

VX-509 100 mg qd up to 24 weeks.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | VX- 509 150 mg qd - Before Escape |
|-----------------------|-----------------------------------|

Reporting group description:

VX-509 150 mg qd up to 24 weeks.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | VX-509 200 mg qd - Before Escape |
|-----------------------|----------------------------------|

Reporting group description:

VX-509 200 mg qd up to 24 weeks.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | VX-509 100 mg bid - Before Escape |
|-----------------------|-----------------------------------|

Reporting group description:

VX-509 100 mg bid up to 24 weeks.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | VX-509 150 mg qd - After Escape |
|-----------------------|---------------------------------|

Reporting group description:

VX-509 150 mg qd up to 24 weeks.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | VX-509 200 mg qd - After Escape |
|-----------------------|---------------------------------|

Reporting group description:

VX-509 200 mg qd up to 24 weeks.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | VX-509 150 mg qd - OLE |
|-----------------------|------------------------|

Reporting group description:

VX-509 150 mg qd up to 104 weeks.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | VX-509 200 mg qd - OLE |
|-----------------------|------------------------|

Reporting group description:

VX-509 200 mg qd up to 104 weeks.

| <b>Serious adverse events</b>                                       | Placebo - Before Escape | VX-509 100 mg qd - Before Escape | VX- 509 150 mg qd - Before Escape |
|---|-------------------------|----------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events                   |                         |                                  |                                   |
| subjects affected / exposed   | 4 / 71 (5.63%)          | 3 / 71 (4.23%)                   | 6 / 72 (8.33%)                    |
| number of deaths (all causes)                                       | 0                       | 0                                | 0                                 |
| number of deaths resulting from adverse events                      | 0                       | 0                                | 0                                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                                  |                                   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Lung neoplasm  |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                                   |                |                |                |
| Deep vein thrombosis                                 |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Surgical and medical procedures                      |                |                |                |
| Umbilical hernia repair                              |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (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          |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders             |                |                |                |
| Breast mass  |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Adenomyosis  |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (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          |
| Chronic obstructive pulmonary disease           |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Interstitial lung disease                       |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory distress                            |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| C-reactive protein increased                    |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| 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  |                |                |                |
| Spinal compression fracture                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tendon rupture                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Cardiac disorders</b>                        |                |                |                |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina pectoris                                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrioventricular block complete                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Right ventricular failure                       |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Nervous system disorders</b>                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Cerebral infarction                             |                |                |                |
| subjects affected / exposed                     | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (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          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vertigo CNS origin                              |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coma  |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Orthostatic intolerance                         |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancytopenia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lymphadenitis                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lymphadenopathy                                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Chorioretinitis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Stomatitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Duodenitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Mallory-Weiss syndrome                          |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Cholelithiasis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (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 and subcutaneous tissue disorders          |                |                |                |
| Panniculitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal colic                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchopneumonia                                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (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          |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Herpes zoster                                   |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sinusitis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peritonitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| 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 tuberculosis                          |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diverticulitis                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocarditis bacterial                          |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | VX-509 200 mg qd -<br>Before Escape | VX-509 100 mg bid -<br>Before Escape | VX-509 150 mg qd -<br>After Escape |
|---|-------------------------------------|--------------------------------------|------------------------------------|
| Total subjects affected by serious adverse events                   |                                     |                                      |                                    |
| subjects affected / exposed   | 5 / 72 (6.94%)                      | 7 / 72 (9.72%)                       | 1 / 29 (3.45%)                     |
| number of deaths (all causes)                                       | 1                                   | 1                                    | 0                                  |
| number of deaths resulting from adverse events                      | 0                                   | 0                                    | 0                                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |                                      |                                    |
| Lung neoplasm   |                                     |                                      |                                    |
| subjects affected / exposed   | 1 / 72 (1.39%)                      | 0 / 72 (0.00%)                       | 0 / 29 (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                              |
| Vascular disorders  |                                     |                                      |                                    |
| Deep vein thrombosis  |                                     |                                      |                                    |
| subjects affected / exposed   | 0 / 72 (0.00%)                      | 0 / 72 (0.00%)                       | 0 / 29 (0.00%)                     |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 0                                | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0                                | 0 / 0                              |
| Surgical and medical procedures                                     |                                     |                                      |                                    |
| Umbilical hernia repair   |                                     |                                      |                                    |
| subjects affected / exposed   | 0 / 72 (0.00%)                      | 0 / 72 (0.00%)                       | 0 / 29 (0.00%)                     |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 0                                | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0                                | 0 / 0                              |
| General disorders and administration site conditions                |                                     |                                      |                                    |
| Pyrexia   |                                     |                                      |                                    |
| subjects affected / exposed   | 1 / 72 (1.39%)                      | 0 / 72 (0.00%)                       | 0 / 29 (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                              |
| Chest pain  |                                     |                                      |                                    |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                            | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Reproductive system and breast disorders</b>        |                |                |                |
| Breast mass  |                |                |                |
| subjects affected / exposed                            | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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          |
| Adenomyosis  |                |                |                |
| subjects affected / exposed                            | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                |                |
| Pulmonary embolism                                     |                |                |                |
| subjects affected / exposed                            | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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 obstructive pulmonary disease                  |                |                |                |
| subjects affected / exposed                            | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (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          |
| Dyspnoea   |                |                |                |
| subjects affected / exposed                            | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Interstitial lung disease                              |                |                |                |
| subjects affected / exposed                            | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory distress                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Investigations</b>                                 |                |                |                |
| C-reactive protein increased                          |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Injury, poisoning and procedural complications</b> |                |                |                |
| Spinal compression fracture                           |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Tendon rupture  |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Cardiac disorders</b>                              |                |                |                |
| Acute myocardial infarction                           |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure                                       |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (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          |
| Angina unstable                                       |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial fibrillation                                   |                |                |                |
| subjects affected / exposed                           | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Angina pectoris                                 |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrioventricular block complete                 |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Right ventricular failure                       |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Cerebral infarction                             |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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          |
| Vertigo CNS origin                              |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (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          |
| Coma  |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Orthostatic intolerance                         |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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          |
| Pancytopenia                                    |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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          |
| Lymphadenitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lymphadenopathy                                 |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Chorioretinitis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (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          |
| Gastrointestinal disorders                      |                |                |                |
| Stomatitis                                      |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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          |
| Duodenitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Mallory-Weiss syndrome                          |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| 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                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Panniculitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal colic                                     |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthritis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Infections and infestations</b>              |                |                |                |
| <b>Bronchitis</b>                               |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Pneumonia</b>                                |                |                |                |
| subjects affected / exposed                     | 2 / 72 (2.78%) | 0 / 72 (0.00%) | 0 / 29 (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          |
| <b>Bronchopneumonia</b>                         |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (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>Cellulitis</b>                               |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Gastroenteritis</b>                          |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Herpes zoster</b>                            |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Sinusitis</b>                                |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Appendicitis</b>                             |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Peritonitis</b>                              |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Pulmonary tuberculosis</b>                   |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Diverticulitis</b>                           |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Endocarditis bacterial</b>                   |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>  | VX-509 200 mg qd -<br>After Escape | VX-509 150 mg qd -<br>OLE | VX-509 200 mg qd -<br>OLE |
|--|------------------------------------|---------------------------|---------------------------|
| <b>Total subjects affected by serious adverse events</b>                   |                                    |                           |                           |
| subjects affected / exposed  | 5 / 64 (7.81%)                     | 6 / 47 (12.77%)           | 22 / 218 (10.09%)         |
| number of deaths (all causes)  | 0                                  | 0                         | 1                         |
| number of deaths resulting from adverse events                             | 0                                  | 0                         | 0                         |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                                    |                           |                           |
| <b>Lung neoplasm</b>   |                                    |                           |                           |
| subjects affected / exposed  | 0 / 64 (0.00%)                     | 0 / 47 (0.00%)            | 0 / 218 (0.00%)           |
| occurrences causally related to treatment / all                            | 0 / 0                              | 0 / 0                     | 0 / 0                     |
| deaths causally related to treatment / all                                 | 0 / 0                              | 0 / 0                     | 0 / 0                     |
| <b>Vascular disorders</b>  |                                    |                           |                           |
| Deep vein thrombosis   |                                    |                           |                           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Surgical and medical procedures</b>                      |                |                |                 |
| Umbilical hernia repair                                     |                |                |                 |
| subjects affected / exposed                                 | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (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>General disorders and administration site conditions</b> |                |                |                 |
| Pyrexia   |                |                |                 |
| subjects affected / exposed                                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0           |
| Chest pain  |                |                |                 |
| subjects affected / exposed                                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Reproductive system and breast disorders</b>             |                |                |                 |
| Breast mass   |                |                |                 |
| subjects affected / exposed                                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0           |
| Adenomyosis   |                |                |                 |
| subjects affected / exposed                                 | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                |                |                 |
| Pulmonary embolism  |                |                |                 |
| subjects affected / exposed                                 | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (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           |
| Chronic obstructive pulmonary disease                       |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                           | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all       | 0 / 0          | 1 / 2          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Dyspnoea</b>                                       |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (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           |
| <b>Interstitial lung disease</b>                      |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Respiratory distress</b>                           |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Investigations</b>                                 |                |                |                 |
| C-reactive protein increased                          |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Injury, poisoning and procedural complications</b> |                |                |                 |
| Spinal compression fracture                           |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| Tendon rupture  |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Cardiac disorders</b>                              |                |                |                 |
| Acute myocardial infarction                           |                |                |                 |
| subjects affected / exposed                           | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| 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                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Angina unstable                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Atrial fibrillation                             |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Angina pectoris                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (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           |
| Atrioventricular block complete                 |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Right ventricular failure                       |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (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           |
| Nervous system disorders                        |                |                |                 |
| Cerebral infarction                             |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ischaemic stroke                                |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Vertigo CNS origin                              |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Coma</b>                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| <b>Orthostatic intolerance</b>                  |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Blood and lymphatic system disorders</b>     |                |                |                 |
| <b>Neutropenia</b>                              |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Pancytopenia</b>                             |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Thrombocytopenia</b>                         |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Lymphadenitis</b>                            |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Lymphadenopathy</b>                          |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Eye disorders</b>                            |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Chorioretinitis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                |                |                 |
| Stomatitis                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Duodenitis                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Intestinal obstruction                          |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Mallory-Weiss syndrome                          |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                |                |                 |
| Cholecystitis                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| 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                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                |                |                 |
| Panniculitis                                    |                |                |                 |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| subjects affected / exposed                            | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (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>Renal and urinary disorders</b>                     |                |                |                 |
| Renal colic  |                |                |                 |
| subjects affected / exposed                            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |                 |
| Arthritis  |                |                |                 |
| subjects affected / exposed                            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| Osteoarthritis   |                |                |                 |
| subjects affected / exposed                            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Infections and infestations</b>                     |                |                |                 |
| Bronchitis   |                |                |                 |
| subjects affected / exposed                            | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia  |                |                |                 |
| subjects affected / exposed                            | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 3 / 218 (1.38%) |
| occurrences causally related to treatment / all        | 0 / 0          | 2 / 2          | 1 / 3           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| Bronchopneumonia                                       |                |                |                 |
| subjects affected / exposed                            | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all        | 1 / 1          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |
| Cellulitis   |                |                |                 |
| subjects affected / exposed                            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Gastroenteritis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Herpes zoster                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sinusitis                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Appendicitis                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Peritonitis                                     |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary tuberculosis                          |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (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           |
| Diverticulitis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Endocarditis bacterial                          |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>  | Placebo - Before Escape | VX-509 100 mg qd - Before Escape | VX- 509 150 mg qd - Before Escape |
|--|-------------------------|----------------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events                      |                         |                                  |                                   |
| subjects affected / exposed  | 29 / 71 (40.85%)        | 36 / 71 (50.70%)                 | 43 / 72 (59.72%)                  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                         |                                  |                                   |
| Benign breast neoplasm   |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 1 / 72 (1.39%)                    |
| occurrences (all)  | 0                       | 0                                | 1                                 |
| Benign lymph node neoplasm   |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 0 / 72 (0.00%)                    |
| occurrences (all)  | 0                       | 0                                | 0                                 |
| Bowen's disease  |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 0 / 72 (0.00%)                    |
| occurrences (all)  | 0                       | 0                                | 0                                 |
| Lung neoplasm  |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 0 / 72 (0.00%)                    |
| occurrences (all)  | 0                       | 0                                | 0                                 |
| Squamous cell carcinoma  |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 0 / 72 (0.00%)                    |
| occurrences (all)  | 0                       | 0                                | 0                                 |
| Thyroid neoplasm   |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 0 / 72 (0.00%)                    |
| occurrences (all)  | 0                       | 0                                | 0                                 |
| <b>Vascular disorders</b>  |                         |                                  |                                   |
| Hypertension   |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 2 / 72 (2.78%)                    |
| occurrences (all)  | 0                       | 0                                | 2                                 |
| Hypotension  |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 1 / 71 (1.41%)                   | 1 / 72 (1.39%)                    |
| occurrences (all)  | 0                       | 1                                | 1                                 |
| Hot flush  |                         |                                  |                                   |
| subjects affected / exposed  | 0 / 71 (0.00%)          | 0 / 71 (0.00%)                   | 1 / 72 (1.39%)                    |
| occurrences (all)  | 0                       | 0                                | 1                                 |
| Blood pressure fluctuation   |                         |                                  |                                   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Haemorrhagic vasculitis                              |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Thrombosis   |                |                |                |
| subjects affected / exposed                          | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Flushing   |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Phlebitis superficial                                |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Orthostatic hypotension                              |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| General disorders and administration site conditions |                |                |                |
| Fatigue  |                |                |                |
| subjects affected / exposed                          | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Malaise  |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)                                    | 0              | 0              | 7              |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                                    | 0              | 0              | 1              |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Chest discomfort                                     |                |                |                |
| subjects affected / exposed                          | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Hunger   |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Non-cardiac chest pain      |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Oedema peripheral           |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Spinal pain                 |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Early satiety               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Influenza like illness      |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Chest pain                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Inflammation                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Oedema                      |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Immune system disorders     |                |                |                |
| Contrast media allergy      |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Hypersensitivity            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Seasonal allergy            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Reproductive system and breast disorders        |                |                |                |
| Breast mass                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Menstruation irregular                          |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Prostatitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Vaginal prolapse                                |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Vulvovaginal burning sensation                  |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Ovarian cyst                                    |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Vaginal haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Adenomyosis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Amenorrhoea                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Menopausal symptoms                             |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Vaginal inflammation                            |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |

|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| Cough                        |                |                |                |
| subjects affected / exposed  | 3 / 71 (4.23%) | 0 / 71 (0.00%) | 5 / 72 (6.94%) |
| occurrences (all)            | 3              | 0              | 5              |
| Oropharyngeal pain           |                |                |                |
| subjects affected / exposed  | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 2 / 72 (2.78%) |
| occurrences (all)            | 1              | 1              | 2              |
| Epistaxis                    |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Dyspnoea                     |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 2              | 0              |
| Nasal congestion             |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)            | 0              | 0              | 1              |
| Pulmonary fibrosis           |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Respiratory tract congestion |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)            | 0              | 0              | 1              |
| Rhinorrhoea                  |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)            | 0              | 0              | 1              |
| Upper-airway cough syndrome  |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Dysphonia                    |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Sinus congestion             |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Lung infiltration            |                |                |                |
| subjects affected / exposed  | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all)       | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Psychiatric disorders  |                     |                     |                     |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 71 (0.00%)<br>0 | 1 / 71 (1.41%)<br>2 | 1 / 72 (1.39%)<br>1 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 71 (1.41%)<br>1 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Depression<br>subjects affected / exposed<br>occurrences (all)               | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Abnormal dreams<br>subjects affected / exposed<br>occurrences (all)          | 0 / 71 (0.00%)<br>0 | 1 / 71 (1.41%)<br>1 | 0 / 72 (0.00%)<br>0 |
| Nervousness<br>subjects affected / exposed<br>occurrences (all)              | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Tension<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)           | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Initial insomnia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Major depression<br>subjects affected / exposed<br>occurrences (all)         | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Investigations   |                     |                     |                     |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 71 (2.82%)<br>2 | 0 / 71 (0.00%)<br>0 | 2 / 72 (2.78%)<br>4 |
| Alanine aminotransferase increased   |                     |                     |                     |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed            | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)                      | 1              | 0              | 3              |
| Blood creatine phosphokinase increased |                |                |                |
| subjects affected / exposed            | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)                      | 0              | 0              | 2              |
| Gamma-glutamyltransferase increased    |                |                |                |
| subjects affected / exposed            | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Aspartate aminotransferase increased   |                |                |                |
| subjects affected / exposed            | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Blood triglycerides increased          |                |                |                |
| subjects affected / exposed            | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 3 / 72 (4.17%) |
| occurrences (all)                      | 0              | 0              | 3              |
| Transaminases increased                |                |                |                |
| subjects affected / exposed            | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)                      | 1              | 1              | 1              |
| Blood lactate dehydrogenase increased  |                |                |                |
| subjects affected / exposed            | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Cardiac murmur                         |                |                |                |
| subjects affected / exposed            | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood pressure increased               |                |                |                |
| subjects affected / exposed            | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                      | 2              | 0              | 0              |
| Electrocardiogram QT prolonged         |                |                |                |
| subjects affected / exposed            | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Human chorionic gonadotropin increased |                |                |                |
| subjects affected / exposed            | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Liver function test abnormal           |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Lymphocyte count increased                  |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                           | 0              | 0              | 1              |
| Neutrophil count increased                  |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                           | 0              | 0              | 2              |
| Platelet count increased                    |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Red blood cell sedimentation rate increased |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Weight decreased                            |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| White blood cell count decreased            |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| White blood cell count increased            |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                           | 0              | 0              | 1              |
| Blood cholesterol increased                 |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Low density lipoprotein increased           |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Candida test positive                       |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Chest X-ray abnormal                        |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Blood prolactin increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Body temperature increased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Lipids increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 71 (1.41%)<br>1 | 2 / 71 (2.82%)<br>2 | 2 / 72 (2.78%)<br>4 |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 71 (0.00%)<br>0 | 1 / 71 (1.41%)<br>1 | 2 / 72 (2.78%)<br>3 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 71 (1.41%)<br>1 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Animal bite<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 71 (1.41%)<br>1 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Bone fissure<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 71 (0.00%)<br>0 | 1 / 71 (1.41%)<br>2 | 0 / 72 (0.00%)<br>0 |
| Excoriation  |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Foot fracture               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Laceration                  |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Post-traumatic pain         |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Skeletal injury             |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 2              |
| Tooth fracture              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Pubis fracture              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Humerus fracture            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Rib fracture                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Ankle fracture              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Arthropod bite              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Meniscus lesion             |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Muscle strain               |                |                |                |

|                                     |                |                |                |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Road traffic accident               |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Spinal compression fracture         |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Upper limb fracture                 |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Vaccination complication            |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Cardiac disorders                   |                |                |                |
| Tachycardia                         |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Atrioventricular block first degree |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Left ventricular hypertrophy        |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Palpitations                        |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 1              | 0              |
| Sinus bradycardia                   |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Ventricular extrasystoles           |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 1              | 0              |
| Angina pectoris                     |                |                |                |
| subjects affected / exposed         | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| Atrial fibrillation            |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Bradycardia                    |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Bundle branch block left       |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Cardiac failure                |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 0              | 1              |
| Mitral valve incompetence      |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 0              | 1              |
| Supraventricular extrasystoles |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Thrombophlebitis               |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Conduction disorder            |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Myocardial ischaemia           |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Nervous system disorders       |                |                |                |
| Headache                       |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 6 / 71 (8.45%) | 7 / 72 (9.72%) |
| occurrences (all)              | 3              | 7              | 17             |
| Dizziness                      |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)              | 0              | 0              | 2              |
| Dysgeusia                      |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Migraine                    |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Somnolence                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Facial nerve disorder       |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Neuropathy peripheral       |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Paraesthesia                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Poor quality sleep          |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Radicular pain              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Sleep paralysis             |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Tension headache            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Polyneuropathy              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Carpal tunnel syndrome      |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cluster headache            |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Hypotonia                                   |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Mental impairment                           |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Presyncope                                  |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Sciatica                                    |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Syncope                                     |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Tremor                                      |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Blood and lymphatic system disorders</b> |                |                |                |
| Anemia                                      |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                           | 0              | 0              | 1              |
| Hypochromic anemia                          |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| Leukopenia                                  |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| Neutropenia                                 |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| Thrombocytopenia                            |                |                |                |
| subjects affected / exposed                 | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Anaemia megaloblastic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Ear and labyrinth disorders   |                     |                     |                     |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Eye disorders   |                     |                     |                     |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 71 (0.00%)<br>0 | 1 / 71 (1.41%)<br>1 | 1 / 72 (1.39%)<br>1 |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 71 (1.41%)<br>1 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Conjunctival ulcer<br>subjects affected / exposed<br>occurrences (all)      | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Glaucoma<br>subjects affected / exposed<br>occurrences (all)                | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Iritis<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Blepharospasm   |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cataract                    |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cataract subcapsular        |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Keratitis                   |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gastrointestinal disorders  |                |                |                |
| Diarrhoea                   |                |                |                |
| subjects affected / exposed | 5 / 71 (7.04%) | 6 / 71 (8.45%) | 4 / 72 (5.56%) |
| occurrences (all)           | 7              | 9              | 4              |
| Nausea                      |                |                |                |
| subjects affected / exposed | 4 / 71 (5.63%) | 2 / 71 (2.82%) | 3 / 72 (4.17%) |
| occurrences (all)           | 4              | 2              | 6              |
| Abdominal pain upper        |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 3 / 72 (4.17%) |
| occurrences (all)           | 1              | 2              | 3              |
| Dyspepsia                   |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)           | 1              | 1              | 1              |
| Vomiting                    |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 3 / 72 (4.17%) |
| occurrences (all)           | 1              | 0              | 3              |
| Gastritis                   |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 71 (2.82%) | 3 / 72 (4.17%) |
| occurrences (all)           | 1              | 2              | 3              |
| Abdominal pain              |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Abdominal discomfort        |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)           | 0              | 0              | 2              |

|                                 |                |                |                |
|---------------------------------|----------------|----------------|----------------|
| Constipation                    |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)               | 0              | 1              | 1              |
| Abdominal pain lower            |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)               | 0              | 0              | 1              |
| Dry mouth                       |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)               | 0              | 1              | 1              |
| Glossodynia                     |                |                |                |
| subjects affected / exposed     | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)               | 1              | 1              | 0              |
| Toothache                       |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Abdominal distension            |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Aphthous stomatitis             |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Flatulence                      |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)               | 0              | 0              | 1              |
| Food poisoning                  |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)               | 0              | 0              | 1              |
| Gastroesophageal reflux disease |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Irritable bowel syndrome        |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Mouth ulceration                |                |                |                |
| subjects affected / exposed     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)               | 0              | 0              | 1              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Peptic ulcer                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Stomatitis                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Tongue ulceration           |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Colitis                     |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cheilitis                   |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hypoaesthesia oral          |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Pancreatitis                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Periodontitis               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hepatobiliary disorders     |                |                |                |
| Hepatomegaly                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperbilirubinaemia         |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Liver disorder              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cholelithiasis              |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| <b>Skin and subcutaneous tissue disorders</b>    |                     |                     |                     |
| <b>Erythema</b>                                  |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 3 / 72 (4.17%)<br>3 |
| <b>Rash</b>                                      |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| <b>Acne</b>                                      |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| <b>Alopecia</b>                                  |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| <b>Dermatitis</b>                                |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| <b>Ecchymosis</b>                                |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 1 / 71 (1.41%)<br>1 | 0 / 72 (0.00%)<br>0 |
| <b>Nail disorder</b>                             |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| <b>Onychoclasia</b>                              |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| <b>Pityriasis rosea</b>                          |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| <b>Pruritus</b>                                  |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| <b>Rash papular</b>                              |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 1 / 71 (1.41%)<br>1 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Skin ulcer                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Swelling face               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dermatitis allergic         |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dermatitis contact          |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dry skin                    |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Actinic keratosis           |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Blister                     |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperhidrosis               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperkeratosis              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Psoriasis                   |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Subcutaneous nodule         |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Urticaria                   |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Renal and urinary disorders                     |                |                |                |
| Leukocyturia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Dysuria   |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)                               | 0              | 1              | 1              |
| Hypertonic bladder                              |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Renal colic                                     |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Nocturia  |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Renal cyst                                      |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Urinary incontinence                            |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 2 / 72 (2.78%) |
| occurrences (all)                               | 0              | 2              | 2              |
| Myalgia   |                |                |                |
| subjects affected / exposed                     | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)                               | 0              | 1              | 1              |
| Rheumatoid arthritis                            |                |                |                |
| subjects affected / exposed                     | 3 / 71 (4.23%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                               | 3              | 0              | 0              |
| Rheumatoid nodule                               |                |                |                |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed    | 2 / 71 (2.82%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)              | 2              | 1              | 0              |
| Intervertebral disc protrusion |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Muscle spasms                  |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Musculoskeletal chest pain     |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)              | 1              | 1              | 0              |
| Musculoskeletal pain           |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 1              | 1              |
| Neck pain                      |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 2              | 0              |
| Arthralgia                     |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Bursitis                       |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Exostosis                      |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Limb discomfort                |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Lumbar spinal stenosis         |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Nodal osteoarthritis           |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 2              | 0              |
| Osteoarthritis                 |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Osteopenia                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Osteoporosis                |                |                |                |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Pain in extremity           |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Rotator cuff syndrome       |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Tendonitis                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Sjogren's syndrome          |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Joint swelling              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Foot deformity              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Spinal column stenosis      |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Arthritis                   |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Flank pain                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Joint instability           |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Metatarsalgia</b>                     |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Musculoskeletal stiffness</b>         |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Osteochondrosis</b>                   |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Spinal osteoarthritis</b>             |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Spondylolisthesis</b>                 |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Temporomandibular joint syndrome</b>  |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| <b>Infections and infestations</b>       |                |                |                |
| <b>Nasopharyngitis</b>                   |                |                |                |
| subjects affected / exposed              | 2 / 71 (2.82%) | 3 / 71 (4.23%) | 1 / 72 (1.39%) |
| occurrences (all)                        | 2              | 7              | 1              |
| <b>Upper respiratory tract infection</b> |                |                |                |
| subjects affected / exposed              | 2 / 71 (2.82%) | 3 / 71 (4.23%) | 1 / 72 (1.39%) |
| occurrences (all)                        | 2              | 3              | 1              |
| <b>Bronchitis</b>                        |                |                |                |
| subjects affected / exposed              | 2 / 71 (2.82%) | 2 / 71 (2.82%) | 3 / 72 (4.17%) |
| occurrences (all)                        | 3              | 2              | 3              |
| <b>Gastroenteritis</b>                   |                |                |                |
| subjects affected / exposed              | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 4 / 72 (5.56%) |
| occurrences (all)                        | 1              | 3              | 5              |
| <b>Sinusitis</b>                         |                |                |                |
| subjects affected / exposed              | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)                        | 0              | 1              | 1              |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| Urinary tract infection        |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 5 / 71 (7.04%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 5              | 1              |
| Pharyngitis                    |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 4 / 72 (5.56%) |
| occurrences (all)              | 1              | 0              | 4              |
| Cystitis                       |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 2              | 0              |
| Herpes zoster                  |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 2              | 1              |
| Rhinitis                       |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 2              | 1              |
| Gastroenteritis viral          |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)              | 0              | 0              | 2              |
| Influenza                      |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)              | 1              | 0              | 2              |
| Respiratory tract infection    |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Herpes simplex                 |                |                |                |
| subjects affected / exposed    | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)              | 0              | 1              | 1              |
| Vaginal infection              |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Viral infection                |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Vulvovaginal mycotic infection |                |                |                |
| subjects affected / exposed    | 1 / 71 (1.41%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)              | 1              | 0              | 1              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Breast infection            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Bronchopneumonia            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Dental fistula              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Furuncle                    |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gastritis viral             |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Genital herpes              |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Laryngitis                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Nail bed infection          |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)           | 0              | 0              | 1              |
| Oral candidiasis            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Oral fungal infection       |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Oral herpes                 |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Otitis media                |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Post procedural infection<br>subjects affected / exposed<br>occurrences (all)         | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Respiratory tract infection viral<br>subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Salmonellosis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Soft tissue infection<br>subjects affected / exposed<br>occurrences (all)             | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Subcutaneous abscess<br>subjects affected / exposed<br>occurrences (all)              | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 |
| Acute sinusitis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Gastrointestinal viral infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Helicobacter infection<br>subjects affected / exposed<br>occurrences (all)            | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Mycotoxicosis               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Paronychia                  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Post procedural cellulitis  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Pneumonia                   |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Acute tonsillitis           |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Borrelia infection          |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Bronchitis viral            |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gastrointestinal infection  |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Onychomycosis               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Rash pustular               |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Staphylococcal infection    |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Tinea pedis                 |                |                |                |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Tracheitis                                |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                         | 0              | 0              | 0              |
| Urinary tract infection bacterial         |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                         | 0              | 0              | 0              |
| <b>Metabolism and nutrition disorders</b> |                |                |                |
| Hypercholesterolaemia                     |                |                |                |
| subjects affected / exposed               | 1 / 71 (1.41%) | 3 / 71 (4.23%) | 5 / 72 (6.94%) |
| occurrences (all)                         | 1              | 3              | 5              |
| Hyperlipidaemia                           |                |                |                |
| subjects affected / exposed               | 1 / 71 (1.41%) | 1 / 71 (1.41%) | 1 / 72 (1.39%) |
| occurrences (all)                         | 1              | 1              | 1              |
| Hypertriglyceridaemia                     |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 2 / 71 (2.82%) | 3 / 72 (4.17%) |
| occurrences (all)                         | 0              | 2              | 3              |
| Dyslipidaemia                             |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 2 / 72 (2.78%) |
| occurrences (all)                         | 0              | 0              | 2              |
| Dehydration                               |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                         | 0              | 0              | 1              |
| Diabetes mellitus                         |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 72 (1.39%) |
| occurrences (all)                         | 0              | 0              | 1              |
| Increased appetite                        |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 0 / 72 (0.00%) |
| occurrences (all)                         | 0              | 1              | 0              |
| Gout                                      |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                         | 0              | 0              | 0              |
| Hypoglycaemia                             |                |                |                |
| subjects affected / exposed               | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 0 / 72 (0.00%) |
| occurrences (all)                         | 0              | 0              | 0              |
| Hypokalaemia                              |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                         | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 71 (0.00%)<br>0 | 0 / 71 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | VX-509 200 mg qd -<br>Before Escape | VX-509 100 mg bid -<br>Before Escape | VX-509 150 mg qd -<br>After Escape |
|---|-------------------------------------|--------------------------------------|------------------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 47 / 72 (65.28%)                    | 41 / 72 (56.94%)                     | 11 / 29 (37.93%)                   |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)                  |                                     |                                      |                                    |
| Benign breast neoplasm<br>subjects affected / exposed<br>occurrences (all)              | 0 / 72 (0.00%)<br>0                 | 0 / 72 (0.00%)<br>0                  | 0 / 29 (0.00%)<br>0                |
| Benign lymph node neoplasm<br>subjects affected / exposed<br>occurrences (all)          | 0 / 72 (0.00%)<br>0                 | 0 / 72 (0.00%)<br>0                  | 0 / 29 (0.00%)<br>0                |
| Bowen's disease<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 72 (0.00%)<br>0                 | 0 / 72 (0.00%)<br>0                  | 0 / 29 (0.00%)<br>0                |
| Lung neoplasm<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 72 (0.00%)<br>0                 | 0 / 72 (0.00%)<br>0                  | 0 / 29 (0.00%)<br>0                |
| Squamous cell carcinoma<br>subjects affected / exposed<br>occurrences (all)             | 0 / 72 (0.00%)<br>0                 | 0 / 72 (0.00%)<br>0                  | 0 / 29 (0.00%)<br>0                |
| Thyroid neoplasm<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 72 (0.00%)<br>0                 | 0 / 72 (0.00%)<br>0                  | 0 / 29 (0.00%)<br>0                |
| Vascular disorders  |                                     |                                      |                                    |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                        | 5 / 72 (6.94%)<br>5                 | 1 / 72 (1.39%)<br>1                  | 0 / 29 (0.00%)<br>0                |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 72 (0.00%)<br>0                 | 1 / 72 (1.39%)<br>1                  | 0 / 29 (0.00%)<br>0                |
| Hot flush   |                                     |                                      |                                    |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 0              | 1              | 0              |
| Blood pressure fluctuation                           |                |                |                |
| subjects affected / exposed                          | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 0              | 1              | 0              |
| Haemorrhagic vasculitis                              |                |                |                |
| subjects affected / exposed                          | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Thrombosis   |                |                |                |
| subjects affected / exposed                          | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Flushing   |                |                |                |
| subjects affected / exposed                          | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Phlebitis superficial                                |                |                |                |
| subjects affected / exposed                          | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Orthostatic hypotension                              |                |                |                |
| subjects affected / exposed                          | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| General disorders and administration site conditions |                |                |                |
| Fatigue  |                |                |                |
| subjects affected / exposed                          | 3 / 72 (4.17%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 4              | 1              | 0              |
| Malaise  |                |                |                |
| subjects affected / exposed                          | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 2              | 0              | 0              |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Chest discomfort                                     |                |                |                |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| <b>Hunger</b>                  |                |                |                |
| subjects affected / exposed    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| <b>Non-cardiac chest pain</b>  |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Oedema peripheral</b>       |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Spinal pain</b>             |                |                |                |
| subjects affected / exposed    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| <b>Early satiety</b>           |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)              | 0              | 0              | 1              |
| <b>Influenza like illness</b>  |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Chest pain</b>              |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Inflammation</b>            |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Oedema</b>                  |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Immune system disorders</b> |                |                |                |
| <b>Contrast media allergy</b>  |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| <b>Hypersensitivity</b>        |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Seasonal allergy                         |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Reproductive system and breast disorders |                |                |                |
| Breast mass                              |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Menstruation irregular                   |                |                |                |
| subjects affected / exposed              | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0              |
| Prostatitis                              |                |                |                |
| subjects affected / exposed              | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0              |
| Vaginal prolapse                         |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Vulvovaginal burning sensation           |                |                |                |
| subjects affected / exposed              | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0              |
| Ovarian cyst                             |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Vaginal haemorrhage                      |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Adenomyosis                              |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Amenorrhoea                              |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Menopausal symptoms                      |                |                |                |
| subjects affected / exposed              | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Vaginal inflammation                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Cough   |                |                |                |
| subjects affected / exposed                     | 4 / 72 (5.56%) | 3 / 72 (4.17%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 4              | 3              | 0              |
| Oropharyngeal pain                              |                |                |                |
| subjects affected / exposed                     | 2 / 72 (2.78%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 2              | 2              | 0              |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 3 / 72 (4.17%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 1              | 4              | 0              |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Nasal congestion                                |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Pulmonary fibrosis                              |                |                |                |
| subjects affected / exposed                     | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Respiratory tract congestion                    |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Rhinorrhoea                                     |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Upper-airway cough syndrome                     |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Dysphonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Sinus congestion                                |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                       | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Lung infiltration<br>subjects affected / exposed<br>occurrences (all)  | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all) | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Psychiatric disorders  |                     |                     |                     |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)            | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Depression<br>subjects affected / exposed<br>occurrences (all)         | 0 / 72 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 | 0 / 29 (0.00%)<br>0 |
| Abnormal dreams<br>subjects affected / exposed<br>occurrences (all)    | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Nervousness<br>subjects affected / exposed<br>occurrences (all)        | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Tension<br>subjects affected / exposed<br>occurrences (all)            | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)     | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Initial insomnia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Major depression<br>subjects affected / exposed<br>occurrences (all)   | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Investigations                         |                |                |                |
| Hepatic enzyme increased               |                |                |                |
| subjects affected / exposed            | 5 / 72 (6.94%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 9              | 2              | 0              |
| Alanine aminotransferase increased     |                |                |                |
| subjects affected / exposed            | 5 / 72 (6.94%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 5              | 1              | 0              |
| Blood creatine phosphokinase increased |                |                |                |
| subjects affected / exposed            | 3 / 72 (4.17%) | 3 / 72 (4.17%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 3              | 3              | 0              |
| Gamma-glutamyltransferase increased    |                |                |                |
| subjects affected / exposed            | 2 / 72 (2.78%) | 4 / 72 (5.56%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 2              | 4              | 0              |
| Aspartate aminotransferase increased   |                |                |                |
| subjects affected / exposed            | 4 / 72 (5.56%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 4              | 1              | 0              |
| Blood triglycerides increased          |                |                |                |
| subjects affected / exposed            | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                      | 1              | 0              | 1              |
| Transaminases increased                |                |                |                |
| subjects affected / exposed            | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Blood lactate dehydrogenase increased  |                |                |                |
| subjects affected / exposed            | 2 / 72 (2.78%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 2              | 1              | 0              |
| Cardiac murmur                         |                |                |                |
| subjects affected / exposed            | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Blood pressure increased               |                |                |                |
| subjects affected / exposed            | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Electrocardiogram QT prolonged         |                |                |                |
| subjects affected / exposed            | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Human chorionic gonadotropin increased      |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Liver function test abnormal                |                |                |                |
| subjects affected / exposed                 | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                           | 1              | 0              | 1              |
| Lymphocyte count increased                  |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Neutrophil count increased                  |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Platelet count increased                    |                |                |                |
| subjects affected / exposed                 | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 1              | 0              | 0              |
| Red blood cell sedimentation rate increased |                |                |                |
| subjects affected / exposed                 | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 1              | 0              | 0              |
| Weight decreased                            |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| White blood cell count decreased            |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| White blood cell count increased            |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| Blood cholesterol increased                 |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                           | 0              | 0              | 1              |
| Low density lipoprotein increased           |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                           | 0              | 0              | 1              |
| Candida test positive                       |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Chest X-ray abnormal                           |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Blood alkaline phosphatase increased           |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Blood prolactin increased                      |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Body temperature increased                     |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Lipids increased                               |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Lymphocyte count decreased                     |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Fall   |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Contusion                                      |                |                |                |
| subjects affected / exposed                    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Ligament sprain                                |                |                |                |
| subjects affected / exposed                    | 1 / 72 (1.39%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 1              | 2              | 0              |
| Animal bite                                    |                |                |                |
| subjects affected / exposed                    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Limb injury                                    |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| <b>Bone fissure</b>         |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Excoriation</b>          |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Foot fracture</b>        |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Laceration</b>           |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Post-traumatic pain</b>  |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Skeletal injury</b>      |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Tooth fracture</b>       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Pubis fracture</b>       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Humerus fracture</b>     |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Rib fracture</b>         |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Ankle fracture</b>       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| <b>Arthropod bite</b>       |                |                |                |

|                                     |                |                |                |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Meniscus lesion                     |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Muscle strain                       |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Road traffic accident               |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Spinal compression fracture         |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Upper limb fracture                 |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Vaccination complication            |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Cardiac disorders                   |                |                |                |
| Tachycardia                         |                |                |                |
| subjects affected / exposed         | 1 / 72 (1.39%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 1              | 2              | 0              |
| Atrioventricular block first degree |                |                |                |
| subjects affected / exposed         | 0 / 72 (0.00%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 0              | 2              | 0              |
| Left ventricular hypertrophy        |                |                |                |
| subjects affected / exposed         | 1 / 72 (1.39%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 1              | 1              | 0              |
| Palpitations                        |                |                |                |
| subjects affected / exposed         | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 1              | 0              | 0              |
| Sinus bradycardia                   |                |                |                |
| subjects affected / exposed         | 1 / 72 (1.39%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                   | 1              | 1              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)      | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)                | 0 / 72 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 | 0 / 29 (0.00%)<br>0 |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)            | 0 / 72 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 | 0 / 29 (0.00%)<br>0 |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Bundle branch block left<br>subjects affected / exposed<br>occurrences (all)       | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Cardiac failure<br>subjects affected / exposed<br>occurrences (all)                | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)      | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Supraventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all) | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Thrombophlebitis<br>subjects affected / exposed<br>occurrences (all)               | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Conduction disorder<br>subjects affected / exposed<br>occurrences (all)            | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Myocardial ischaemia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Nervous system disorders<br>Headache   |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 6 / 72 (8.33%) | 6 / 72 (8.33%) | 0 / 29 (0.00%) |
| occurrences (all)           | 21             | 6              | 0              |
| Dizziness                   |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Dysgeusia                   |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 2              | 0              |
| Migraine                    |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Somnolence                  |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Facial nerve disorder       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Neuropathy peripheral       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Paraesthesia                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Poor quality sleep          |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Radicular pain              |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Sleep paralysis             |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Tension headache            |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Polyneuropathy              |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                           | 0              | 0              | 1              |
| <b>Carpal tunnel syndrome</b>               |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Cluster headache</b>                     |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Hypotonia</b>                            |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Mental impairment</b>                    |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Presyncope</b>                           |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Sciatica</b>                             |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Syncope</b>                              |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Tremor</b>                               |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Blood and lymphatic system disorders</b> |                |                |                |
| <b>Anaemia</b>                              |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Hypochromic anaemia</b>                  |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |
| <b>Leukopenia</b>                           |                |                |                |
| subjects affected / exposed                 | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Neutropenia                 |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Thrombocytopenia            |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Lymphopenia                 |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Anaemia megaloblastic       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Ear and labyrinth disorders |                |                |                |
| Ear pain                    |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Tinnitus                    |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Vertigo                     |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Eye disorders               |                |                |                |
| Conjunctivitis              |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Dry eye                     |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Conjunctivitis allergic     |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Conjunctival ulcer          |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)           | 0              | 0              | 1              |
| Glaucoma                    |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Iritis                      |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)           | 0              | 0              | 1              |
| Blepharospasm               |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cataract                    |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cataract subcapsular        |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Keratitis                   |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gastrointestinal disorders  |                |                |                |
| Diarrhoea                   |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 2              | 0              |
| Nausea                      |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 3 / 72 (4.17%) | 1 / 29 (3.45%) |
| occurrences (all)           | 8              | 3              | 1              |
| Abdominal pain upper        |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Dyspepsia                   |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 2              | 0              |
| Vomiting                    |                |                |                |
| subjects affected / exposed | 3 / 72 (4.17%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 6              | 0              | 0              |
| Gastritis                   |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|                                  |                |                |                |
|----------------------------------|----------------|----------------|----------------|
| Abdominal pain                   |                |                |                |
| subjects affected / exposed      | 2 / 72 (2.78%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                | 3              | 1              | 0              |
| Abdominal discomfort             |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 1              | 0              |
| Constipation                     |                |                |                |
| subjects affected / exposed      | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 1              | 0              | 0              |
| Abdominal pain lower             |                |                |                |
| subjects affected / exposed      | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 1              | 0              | 0              |
| Dry mouth                        |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Glossodynia                      |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Toothache                        |                |                |                |
| subjects affected / exposed      | 2 / 72 (2.78%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 2              | 0              | 0              |
| Abdominal distension             |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Aphthous stomatitis              |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 1              | 0              |
| Flatulence                       |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Food poisoning                   |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Gastrooesophageal reflux disease |                |                |                |
| subjects affected / exposed      | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Irritable bowel syndrome    |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Mouth ulceration            |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Peptic ulcer                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Stomatitis                  |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Tongue ulceration           |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Colitis                     |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cheilitis                   |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hypoaesthesia oral          |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Pancreatitis                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Periodontitis               |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hepatobiliary disorders     |                |                |                |
| Hepatomegaly                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperbilirubinaemia         |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                     | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Liver disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| <b>Skin and subcutaneous tissue disorders</b>                        |                     |                     |                     |
| Erythema<br>subjects affected / exposed<br>occurrences (all)         | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1 |
| Rash<br>subjects affected / exposed<br>occurrences (all)             | 2 / 72 (2.78%)<br>2 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Acne<br>subjects affected / exposed<br>occurrences (all)             | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 72 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 | 0 / 29 (0.00%)<br>0 |
| Ecchymosis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all)    | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Onychoclasia<br>subjects affected / exposed<br>occurrences (all)     | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Pityriasis rosea<br>subjects affected / exposed<br>occurrences (all) | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Pruritus                    |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Rash papular                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Skin ulcer                  |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Swelling face               |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Dermatitis allergic         |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dermatitis contact          |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dry skin                    |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Actinic keratosis           |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Blister                     |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperhidrosis               |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperkeratosis              |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Psoriasis                   |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Subcutaneous nodule<br>subjects affected / exposed<br>occurrences (all)  | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)            | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| <b>Renal and urinary disorders</b>                                       |                     |                     |                     |
| Leukocyturia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 72 (2.78%)<br>2 | 1 / 72 (1.39%)<br>2 | 1 / 29 (3.45%)<br>1 |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)              | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1 |
| Hypertonic bladder<br>subjects affected / exposed<br>occurrences (all)   | 1 / 72 (1.39%)<br>1 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Renal colic<br>subjects affected / exposed<br>occurrences (all)          | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)           | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Nocturia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Renal cyst<br>subjects affected / exposed<br>occurrences (all)           | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| <b>Musculoskeletal and connective tissue disorders</b>                   |                     |                     |                     |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 2 / 72 (2.78%)<br>2 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Myalgia  |                     |                     |                     |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Rheumatoid arthritis           |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Rheumatoid nodule              |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Intervertebral disc protrusion |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 2              | 0              |
| Muscle spasms                  |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Musculoskeletal chest pain     |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Musculoskeletal pain           |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Neck pain                      |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Arthralgia                     |                |                |                |
| subjects affected / exposed    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Bursitis                       |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Exostosis                      |                |                |                |
| subjects affected / exposed    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Limb discomfort                |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Lumbar spinal stenosis         |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Nodal osteoarthritis        |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Osteoarthritis              |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Osteopenia                  |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Osteoporosis                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Pain in extremity           |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Rotator cuff syndrome       |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Tendonitis                  |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Sjogren's syndrome          |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)           | 0              | 0              | 1              |
| Joint swelling              |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Foot deformity              |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Spinal column stenosis      |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Arthritis                   |                |                |                |

|                                   |                |                |                |
|-----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Flank pain                        |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Joint instability                 |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Metatarsalgia                     |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Musculoskeletal stiffness         |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Osteochondrosis                   |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Spinal osteoarthritis             |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Spondylolisthesis                 |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Temporomandibular joint syndrome  |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Infections and infestations       |                |                |                |
| Nasopharyngitis                   |                |                |                |
| subjects affected / exposed       | 4 / 72 (5.56%) | 3 / 72 (4.17%) | 1 / 29 (3.45%) |
| occurrences (all)                 | 4              | 4              | 1              |
| Upper respiratory tract infection |                |                |                |
| subjects affected / exposed       | 3 / 72 (4.17%) | 3 / 72 (4.17%) | 1 / 29 (3.45%) |
| occurrences (all)                 | 3              | 3              | 1              |
| Bronchitis                        |                |                |                |
| subjects affected / exposed       | 4 / 72 (5.56%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                 | 4              | 0              | 1              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Gastroenteritis             |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Sinusitis                   |                |                |                |
| subjects affected / exposed | 3 / 72 (4.17%) | 2 / 72 (2.78%) | 0 / 29 (0.00%) |
| occurrences (all)           | 3              | 3              | 0              |
| Urinary tract infection     |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Pharyngitis                 |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)           | 1              | 0              | 1              |
| Cystitis                    |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Herpes zoster               |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Rhinitis                    |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Gastroenteritis viral       |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Influenza                   |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Respiratory tract infection |                |                |                |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Herpes simplex              |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Vaginal infection           |                |                |                |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| Viral infection                |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 1 / 29 (3.45%) |
| occurrences (all)              | 0              | 1              | 1              |
| Vulvovaginal mycotic infection |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Breast infection               |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Bronchopneumonia               |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Dental fistula                 |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Furuncle                       |                |                |                |
| subjects affected / exposed    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 2              | 0              | 0              |
| Gastritis viral                |                |                |                |
| subjects affected / exposed    | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Genital herpes                 |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Laryngitis                     |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Nail bed infection             |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |
| Oral candidiasis               |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Oral fungal infection          |                |                |                |
| subjects affected / exposed    | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)              | 0              | 0              | 0              |

|                                   |                |                |                |
|-----------------------------------|----------------|----------------|----------------|
| Oral herpes                       |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 2              | 0              |
| Otitis media                      |                |                |                |
| subjects affected / exposed       | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 2              | 0              | 0              |
| Post procedural infection         |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 1              | 0              |
| Respiratory tract infection viral |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Salmonellosis                     |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 1 / 72 (1.39%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 1              | 0              |
| Soft tissue infection             |                |                |                |
| subjects affected / exposed       | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 1              | 0              | 0              |
| Subcutaneous abscess              |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Tonsillitis                       |                |                |                |
| subjects affected / exposed       | 1 / 72 (1.39%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 1              | 0              | 0              |
| Tooth abscess                     |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Tooth infection                   |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Acute sinusitis                   |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Gastrointestinal viral infection  |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |

|                                   |                |                |                |
|-----------------------------------|----------------|----------------|----------------|
| Helicobacter infection            |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Lower respiratory tract infection |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Mycotoxycosis                     |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                 | 0              | 0              | 1              |
| Paronychia                        |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Post procedural cellulitis        |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Pneumonia                         |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Acute tonsillitis                 |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Borrelia infection                |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Bronchitis viral                  |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Gastrointestinal infection        |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Onychomycosis                     |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |
| Rash pustular                     |                |                |                |
| subjects affected / exposed       | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0              |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Staphylococcal infection<br>subjects affected / exposed<br>occurrences (all)          | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Tinea pedis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Tracheitis<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Urinary tract infection bacterial<br>subjects affected / exposed<br>occurrences (all) | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Metabolism and nutrition disorders  |                     |                     |                     |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)             | 3 / 72 (4.17%)<br>3 | 4 / 72 (5.56%)<br>4 | 1 / 29 (3.45%)<br>1 |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 72 (2.78%)<br>2 | 2 / 72 (2.78%)<br>2 | 1 / 29 (3.45%)<br>1 |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 72 (0.00%)<br>0 | 1 / 72 (1.39%)<br>1 | 0 / 29 (0.00%)<br>0 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all)                | 0 / 72 (0.00%)<br>0 | 0 / 72 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Gout  |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hypoglycaemia               |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hypokalaemia                |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Vitamin D deficiency        |                |                |                |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 72 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

| <b>Non-serious adverse events</b>                                   | VX-509 200 mg qd -<br>After Escape | VX-509 150 mg qd -<br>OLE | VX-509 200 mg qd -<br>OLE |
|---|------------------------------------|---------------------------|---------------------------|
| Total subjects affected by non-serious adverse events               |                                    |                           |                           |
| subjects affected / exposed   | 36 / 64 (56.25%)                   | 28 / 47 (59.57%)          | 118 / 218 (54.13%)        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                    |                           |                           |
| Benign breast neoplasm  |                                    |                           |                           |
| subjects affected / exposed   | 0 / 64 (0.00%)                     | 0 / 47 (0.00%)            | 0 / 218 (0.00%)           |
| occurrences (all)   | 0                                  | 0                         | 0                         |
| Benign lymph node neoplasm  |                                    |                           |                           |
| subjects affected / exposed   | 0 / 64 (0.00%)                     | 0 / 47 (0.00%)            | 1 / 218 (0.46%)           |
| occurrences (all)   | 0                                  | 0                         | 1                         |
| Bowen's disease   |                                    |                           |                           |
| subjects affected / exposed   | 0 / 64 (0.00%)                     | 0 / 47 (0.00%)            | 1 / 218 (0.46%)           |
| occurrences (all)   | 0                                  | 0                         | 1                         |
| Lung neoplasm   |                                    |                           |                           |
| subjects affected / exposed   | 0 / 64 (0.00%)                     | 0 / 47 (0.00%)            | 1 / 218 (0.46%)           |
| occurrences (all)   | 0                                  | 0                         | 1                         |
| Squamous cell carcinoma   |                                    |                           |                           |
| subjects affected / exposed   | 0 / 64 (0.00%)                     | 1 / 47 (2.13%)            | 0 / 218 (0.00%)           |
| occurrences (all)   | 0                                  | 1                         | 0                         |
| Thyroid neoplasm  |                                    |                           |                           |
| subjects affected / exposed   | 0 / 64 (0.00%)                     | 0 / 47 (0.00%)            | 1 / 218 (0.46%)           |
| occurrences (all)   | 0                                  | 0                         | 1                         |
| Vascular disorders  |                                    |                           |                           |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Hypertension   |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 2 / 47 (4.26%) | 8 / 218 (3.67%) |
| occurrences (all)                                    | 0              | 2              | 9               |
| Hypotension  |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0               |
| Hot flush  |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0               |
| Blood pressure fluctuation                           |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0               |
| Haemorrhagic vasculitis                              |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0               |
| Thrombosis   |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0               |
| Flushing   |                |                |                 |
| subjects affected / exposed                          | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0               |
| Phlebitis superficial                                |                |                |                 |
| subjects affected / exposed                          | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                                    | 1              | 0              | 1               |
| Orthostatic hypotension                              |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                                    | 0              | 0              | 1               |
| General disorders and administration site conditions |                |                |                 |
| Fatigue  |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                                    | 0              | 0              | 1               |
| Malaise  |                |                |                 |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0               |
| Pyrexia  |                |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Asthenia                    |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 5 / 218 (2.29%) |
| occurrences (all)           | 1              | 1              | 5               |
| Chest discomfort            |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Hunger                      |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Non-cardiac chest pain      |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Oedema peripheral           |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 1              | 1              | 0               |
| Spinal pain                 |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Early satiety               |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Influenza like illness      |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 1              | 1               |
| Chest pain                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Inflammation                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Oedema                      |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Immune system disorders     |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Contrast media allergy                          |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Hypersensitivity                                |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Seasonal allergy                                |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                               | 0              | 1              | 2               |
| <b>Reproductive system and breast disorders</b> |                |                |                 |
| Breast mass                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Menstruation irregular                          |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Prostatitis                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 1               |
| Vaginal prolapse                                |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Vulvovaginal burning sensation                  |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Ovarian cyst                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0               |
| Vaginal haemorrhage                             |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 1              | 1               |
| Adenomyosis                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0               |
| Amenorrhoea                                     |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 1               |
| Menopausal symptoms                             |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 1               |
| Vaginal inflammation                            |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 1               |
| Respiratory, thoracic and mediastinal disorders |                |                |                 |
| Cough   |                |                |                 |
| subjects affected / exposed                     | 2 / 64 (3.13%) | 0 / 47 (0.00%) | 9 / 218 (4.13%) |
| occurrences (all)                               | 2              | 0              | 10              |
| Oropharyngeal pain                              |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                               | 1              | 1              | 2               |
| Epistaxis                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0               |
| Dyspnoea  |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 1              | 1               |
| Nasal congestion                                |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 2               |
| Pulmonary fibrosis                              |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Respiratory tract congestion                    |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 1               |
| Rhinorrhoea                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Upper-airway cough syndrome                     |                |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Dysphonia                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Sinus congestion            |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Lung infiltration           |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Pulmonary embolism          |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Psychiatric disorders       |                |                |                 |
| Insomnia                    |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Anxiety                     |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Depression                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Abnormal dreams             |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Nervousness                 |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 1              | 0              | 0               |
| Tension                     |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Depressed mood              |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 1              | 0              | 1               |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Initial insomnia<br>subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)  | 0              | 0              | 1               |
| Major depression<br>subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)  | 0              | 0              | 1               |
| <b>Investigations</b>  |                |                |                 |
| Hepatic enzyme increased<br>subjects affected / exposed                  | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)  | 0              | 0              | 2               |
| Alanine aminotransferase increased<br>subjects affected / exposed        | 1 / 64 (1.56%) | 2 / 47 (4.26%) | 5 / 218 (2.29%) |
| occurrences (all)  | 1              | 2              | 6               |
| Blood creatine phosphokinase<br>increased<br>subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 3 / 218 (1.38%) |
| occurrences (all)  | 0              | 3              | 3               |
| Gamma-glutamyltransferase<br>increased<br>subjects affected / exposed    | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 4 / 218 (1.83%) |
| occurrences (all)  | 0              | 1              | 5               |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed   | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 4 / 218 (1.83%) |
| occurrences (all)  | 1              | 1              | 4               |
| Blood triglycerides increased<br>subjects affected / exposed             | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)  | 1              | 0              | 1               |
| Transaminases increased<br>subjects affected / exposed                   | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)  | 0              | 0              | 0               |
| Blood lactate dehydrogenase<br>increased<br>subjects affected / exposed  | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 3 / 218 (1.38%) |
| occurrences (all)  | 0              | 1              | 3               |
| Cardiac murmur<br>subjects affected / exposed                            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)  | 0              | 0              | 0               |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Blood pressure increased                    |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)                           | 0              | 0              | 2               |
| Electrocardiogram QT prolonged              |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| Human chorionic gonadotropin increased      |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| Liver function test abnormal                |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                           | 0              | 0              | 1               |
| Lymphocyte count increased                  |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| Neutrophil count increased                  |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| Platelet count increased                    |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| Red blood cell sedimentation rate increased |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)                           | 0              | 2              | 1               |
| Weight decreased                            |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                           | 0              | 0              | 1               |
| White blood cell count decreased            |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| White blood cell count increased            |                |                |                 |
| subjects affected / exposed                 | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                           | 0              | 0              | 0               |
| Blood cholesterol increased                 |                |                |                 |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| subjects affected / exposed                    | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                              | 1              | 1              | 2               |
| Low density lipoprotein increased              |                |                |                 |
| subjects affected / exposed                    | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 3 / 218 (1.38%) |
| occurrences (all)                              | 1              | 1              | 4               |
| Candida test positive                          |                |                |                 |
| subjects affected / exposed                    | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0               |
| Chest X-ray abnormal                           |                |                |                 |
| subjects affected / exposed                    | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                              | 1              | 0              | 1               |
| Blood alkaline phosphatase increased           |                |                |                 |
| subjects affected / exposed                    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                              | 0              | 0              | 1               |
| Blood prolactin increased                      |                |                |                 |
| subjects affected / exposed                    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                              | 0              | 0              | 1               |
| Body temperature increased                     |                |                |                 |
| subjects affected / exposed                    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                              | 0              | 0              | 1               |
| Lipids increased                               |                |                |                 |
| subjects affected / exposed                    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                              | 0              | 0              | 1               |
| Lymphocyte count decreased                     |                |                |                 |
| subjects affected / exposed                    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                              | 0              | 0              | 1               |
| Injury, poisoning and procedural complications |                |                |                 |
| Fall   |                |                |                 |
| subjects affected / exposed                    | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 4 / 218 (1.83%) |
| occurrences (all)                              | 0              | 2              | 4               |
| Contusion                                      |                |                |                 |
| subjects affected / exposed                    | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                              | 1              | 1              | 3               |
| Ligament sprain                                |                |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 2 / 47 (4.26%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 2              | 2               |
| Animal bite                 |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Limb injury                 |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Bone fissure                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Excoriation                 |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Foot fracture               |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Laceration                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Post-traumatic pain         |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Skeletal injury             |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Tooth fracture              |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 1              | 1              | 0               |
| Pubis fracture              |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 1              | 0              | 0               |
| Humerus fracture            |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 1              | 1               |
| Rib fracture                |                |                |                 |

|                                     |                |                |                 |
|-------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)                   | 0              | 0              | 2               |
| Ankle fracture                      |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)                   | 0              | 1              | 0               |
| Arthropod bite                      |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Meniscus lesion                     |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Muscle strain                       |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Road traffic accident               |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)                   | 0              | 1              | 0               |
| Spinal compression fracture         |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Upper limb fracture                 |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Vaccination complication            |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Cardiac disorders                   |                |                |                 |
| Tachycardia                         |                |                |                 |
| subjects affected / exposed         | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                   | 1              | 0              | 1               |
| Atrioventricular block first degree |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 3 / 218 (1.38%) |
| occurrences (all)                   | 0              | 0              | 4               |
| Left ventricular hypertrophy        |                |                |                 |
| subjects affected / exposed         | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0               |

|                                |                |                |                 |
|--------------------------------|----------------|----------------|-----------------|
| Palpitations                   |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)              | 0              | 1              | 1               |
| Sinus bradycardia              |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 5 / 218 (2.29%) |
| occurrences (all)              | 0              | 0              | 5               |
| Ventricular extrasystoles      |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Angina pectoris                |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Atrial fibrillation            |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)              | 0              | 0              | 2               |
| Bradycardia                    |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Bundle branch block left       |                |                |                 |
| subjects affected / exposed    | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 1              | 0              | 0               |
| Cardiac failure                |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)              | 0              | 1              | 1               |
| Mitral valve incompetence      |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Supraventricular extrasystoles |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Thrombophlebitis               |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Conduction disorder            |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)              | 0              | 0              | 1               |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Myocardial ischaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| <b>Nervous system disorders</b>   |                     |                     |                      |
| Headache<br>subjects affected / exposed<br>occurrences (all)              | 2 / 64 (3.13%)<br>2 | 0 / 47 (0.00%)<br>0 | 6 / 218 (2.75%)<br>6 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)             | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Migraine<br>subjects affected / exposed<br>occurrences (all)              | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 3 / 218 (1.38%)<br>4 |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)            | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| Facial nerve disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 64 (1.56%)<br>1 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| Poor quality sleep<br>subjects affected / exposed<br>occurrences (all)    | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Radicular pain<br>subjects affected / exposed<br>occurrences (all)        | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Sleep paralysis   |                     |                     |                      |

|                                      |                |                |                 |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0               |
| Tension headache                     |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0               |
| Polyneuropathy                       |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0               |
| Carpal tunnel syndrome               |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Cluster headache                     |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Hypotonia                            |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Mental impairment                    |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Presyncope                           |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Sciatica                             |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 2               |
| Syncope                              |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Tremor                               |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                    | 0              | 0              | 1               |
| Blood and lymphatic system disorders |                |                |                 |
| Anaemia                              |                |                |                 |
| subjects affected / exposed          | 0 / 64 (0.00%) | 2 / 47 (4.26%) | 2 / 218 (0.92%) |
| occurrences (all)                    | 0              | 2              | 2               |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Hypochromic anaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 64 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 | 0 / 218 (0.00%)<br>0 |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 64 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 | 1 / 218 (0.46%)<br>1 |
| Anaemia megaloblastic<br>subjects affected / exposed<br>occurrences (all) | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| Ear and labyrinth disorders   |                     |                     |                      |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)              | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)               | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0 |
| Eye disorders   |                     |                     |                      |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 64 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 | 0 / 218 (0.00%)<br>0 |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)               | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1 |
| Conjunctivitis allergic   |                     |                     |                      |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Conjunctival ulcer          |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 2               |
| Glaucoma                    |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 1              | 0              | 0               |
| Iritis                      |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Blepharospasm               |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Cataract                    |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Cataract subcapsular        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Keratitis                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Gastrointestinal disorders  |                |                |                 |
| Diarrhoea                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 2 / 47 (4.26%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 3              | 3               |
| Nausea                      |                |                |                 |
| subjects affected / exposed | 2 / 64 (3.13%) | 1 / 47 (2.13%) | 3 / 218 (1.38%) |
| occurrences (all)           | 2              | 1              | 5               |
| Abdominal pain upper        |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)           | 1              | 1              | 2               |
| Dyspepsia                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Vomiting                    |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 2 / 47 (4.26%) | 1 / 218 (0.46%) |
| occurrences (all)           | 1              | 2              | 1               |
| Gastritis                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 1              | 2               |
| Abdominal pain              |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 1              | 1               |
| Abdominal discomfort        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Constipation                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Abdominal pain lower        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Dry mouth                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Glossodynia                 |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Toothache                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Abdominal distension        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Aphthous stomatitis         |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Flatulence                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |

|                                 |                |                |                 |
|---------------------------------|----------------|----------------|-----------------|
| Food poisoning                  |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 0              | 0              | 0               |
| Gastroesophageal reflux disease |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)               | 0              | 1              | 2               |
| Irritable bowel syndrome        |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 0              | 0              | 0               |
| Mouth ulceration                |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 0              | 0              | 0               |
| Peptic ulcer                    |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 0              | 0              | 0               |
| Stomatitis                      |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 0              | 0              | 0               |
| Tongue ulceration               |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 0              | 0              | 0               |
| Colitis                         |                |                |                 |
| subjects affected / exposed     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)               | 1              | 0              | 0               |
| Cheilitis                       |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)               | 0              | 0              | 1               |
| Hypoaesthesia oral              |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)               | 0              | 0              | 1               |
| Pancreatitis                    |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)               | 0              | 0              | 1               |
| Periodontitis                   |                |                |                 |
| subjects affected / exposed     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)               | 0              | 0              | 1               |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Hepatobiliary disorders                |                |                |                 |
| Hepatomegaly                           |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Hyperbilirubinaemia                    |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Liver disorder                         |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Cholelithiasis                         |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Skin and subcutaneous tissue disorders |                |                |                 |
| Erythema                               |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)                      | 0              | 0              | 2               |
| Rash                                   |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 2 / 47 (4.26%) | 3 / 218 (1.38%) |
| occurrences (all)                      | 0              | 2              | 3               |
| Acne                                   |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0               |
| Alopecia                               |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Dermatitis                             |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0               |
| Ecchymosis                             |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Nail disorder                          |                |                |                 |
| subjects affected / exposed            | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0               |
| Onychoclasia                           |                |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Pityriasis rosea            |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Pruritus                    |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Rash papular                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Skin ulcer                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Swelling face               |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Dermatitis allergic         |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 1              | 0              | 2               |
| Dermatitis contact          |                |                |                 |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 1              | 0              | 1               |
| Dry skin                    |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 2               |
| Actinic keratosis           |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Blister                     |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Hyperhidrosis               |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 3               |
| Hyperkeratosis              |                |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Psoriasis                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Subcutaneous nodule         |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Urticaria                   |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Renal and urinary disorders |                |                |                 |
| Leukocyturia                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)           | 0              | 0              | 5               |
| Dysuria                     |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Hypertonic bladder          |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Renal colic                 |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 1              | 1               |
| Haematuria                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Nocturia                    |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Renal cyst                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Urinary incontinence        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Back pain                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 6 / 218 (2.75%) |
| occurrences (all)                               | 0              | 0              | 6               |
| Myalgia   |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0               |
| Rheumatoid arthritis                            |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 6 / 218 (2.75%) |
| occurrences (all)                               | 0              | 1              | 6               |
| Rheumatoid nodule                               |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Intervertebral disc protrusion                  |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Muscle spasms                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)                               | 0              | 0              | 2               |
| Musculoskeletal chest pain                      |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0               |
| Musculoskeletal pain                            |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                               | 0              | 1              | 2               |
| Neck pain                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                               | 0              | 0              | 2               |
| Arthralgia                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 2 / 47 (4.26%) | 3 / 218 (1.38%) |
| occurrences (all)                               | 1              | 2              | 3               |
| Bursitis  |                |                |                 |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)                               | 1              | 0              | 2               |
| Exostosis                                       |                |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Limb discomfort             |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Lumbar spinal stenosis      |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Nodal osteoarthritis        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Osteoarthritis              |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 3 / 218 (1.38%) |
| occurrences (all)           | 0              | 0              | 3               |
| Osteopenia                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Osteoporosis                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 1              | 0               |
| Rotator cuff syndrome       |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Tendonitis                  |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)           | 0              | 0              | 0               |
| Sjogren's syndrome          |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Joint swelling              |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 2 / 47 (4.26%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 2              | 1               |
| Foot deformity              |                |                |                 |

|                                  |                |                |                  |
|----------------------------------|----------------|----------------|------------------|
| subjects affected / exposed      | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 1              | 1                |
| Spinal column stenosis           |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 1              | 1                |
| Arthritis                        |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Flank pain                       |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Joint instability                |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Metatarsalgia                    |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Musculoskeletal stiffness        |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Osteochondrosis                  |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Spinal osteoarthritis            |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Spondylolisthesis                |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Temporomandibular joint syndrome |                |                |                  |
| subjects affected / exposed      | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                | 0              | 0              | 1                |
| Infections and infestations      |                |                |                  |
| Nasopharyngitis                  |                |                |                  |
| subjects affected / exposed      | 1 / 64 (1.56%) | 2 / 47 (4.26%) | 12 / 218 (5.50%) |
| occurrences (all)                | 1              | 3              | 19               |

|   |                     |                     |                        |
|---|---------------------|---------------------|------------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 64 (1.56%)<br>1 | 2 / 47 (4.26%)<br>2 | 13 / 218 (5.96%)<br>15 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 64 (4.69%)<br>3 | 0 / 47 (0.00%)<br>0 | 12 / 218 (5.50%)<br>14 |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 64 (0.00%)<br>0 | 0 / 47 (0.00%)<br>0 | 2 / 218 (0.92%)<br>2   |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 64 (1.56%)<br>1 | 0 / 47 (0.00%)<br>0 | 5 / 218 (2.29%)<br>5   |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 3 / 64 (4.69%)<br>3 | 1 / 47 (2.13%)<br>1 | 5 / 218 (2.29%)<br>6   |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 64 (1.56%)<br>1 | 2 / 47 (4.26%)<br>2 | 1 / 218 (0.46%)<br>1   |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 64 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 | 0 / 218 (0.00%)<br>0   |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 64 (1.56%)<br>1 | 0 / 47 (0.00%)<br>0 | 8 / 218 (3.67%)<br>8   |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 64 (1.56%)<br>1 | 1 / 47 (2.13%)<br>1 | 1 / 218 (0.46%)<br>2   |
| Gastroenteritis viral<br>subjects affected / exposed<br>occurrences (all)             | 1 / 64 (1.56%)<br>1 | 0 / 47 (0.00%)<br>0 | 1 / 218 (0.46%)<br>1   |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 64 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 | 2 / 218 (0.92%)<br>2   |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 64 (1.56%)<br>1 | 0 / 47 (0.00%)<br>0 | 0 / 218 (0.00%)<br>0   |

|                                |                |                |                 |
|--------------------------------|----------------|----------------|-----------------|
| Herpes simplex                 |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 2 / 218 (0.92%) |
| occurrences (all)              | 0              | 0              | 2               |
| Vaginal infection              |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Viral infection                |                |                |                 |
| subjects affected / exposed    | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 3 / 218 (1.38%) |
| occurrences (all)              | 1              | 0              | 3               |
| Vulvovaginal mycotic infection |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)              | 0              | 0              | 5               |
| Breast infection               |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Bronchopneumonia               |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Dental fistula                 |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Furuncle                       |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Gastritis viral                |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Genital herpes                 |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |
| Laryngitis                     |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)              | 0              | 0              | 1               |
| Nail bed infection             |                |                |                 |
| subjects affected / exposed    | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)              | 0              | 0              | 0               |

|                                   |                |                |                 |
|-----------------------------------|----------------|----------------|-----------------|
| Oral candidiasis                  |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                 | 0              | 1              | 2               |
| Oral fungal infection             |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Oral herpes                       |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Otitis media                      |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Post procedural infection         |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Respiratory tract infection viral |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Salmonellosis                     |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Soft tissue infection             |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Subcutaneous abscess              |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Tonsillitis                       |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Tooth abscess                     |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Tooth infection                   |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 1 / 47 (2.13%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 1              | 1              | 1               |

|                                   |                |                |                 |
|-----------------------------------|----------------|----------------|-----------------|
| Acute sinusitis                   |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 1              | 0              | 0               |
| Gastrointestinal viral infection  |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 1              | 0              | 0               |
| Helicobacter infection            |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 1              | 0              | 0               |
| Lower respiratory tract infection |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 2              | 0              | 0               |
| Mycotoxycosis                     |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 0              | 0               |
| Paronychia                        |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 1              | 0              | 1               |
| Post procedural cellulitis        |                |                |                 |
| subjects affected / exposed       | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 1              | 0              | 0               |
| Pneumonia                         |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 2 / 218 (0.92%) |
| occurrences (all)                 | 0              | 1              | 2               |
| Acute tonsillitis                 |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Borrelia infection                |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Bronchitis viral                  |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%) |
| occurrences (all)                 | 0              | 1              | 0               |
| Gastrointestinal infection        |                |                |                 |
| subjects affected / exposed       | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)                 | 0              | 0              | 1               |

|   |                |                |                  |
|---|----------------|----------------|------------------|
| Onychomycosis                             |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                         | 0              | 0              | 1                |
| Rash pustular                             |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                         | 0              | 0              | 3                |
| Staphylococcal infection                  |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                         | 0              | 0              | 1                |
| Tinea pedis                               |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%)  |
| occurrences (all)                         | 0              | 0              | 1                |
| Tracheitis                                |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%)  |
| occurrences (all)                         | 0              | 1              | 0                |
| Urinary tract infection bacterial         |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 1 / 47 (2.13%) | 0 / 218 (0.00%)  |
| occurrences (all)                         | 0              | 1              | 0                |
| <b>Metabolism and nutrition disorders</b> |                |                |                  |
| Hypercholesterolaemia                     |                |                |                  |
| subjects affected / exposed               | 3 / 64 (4.69%) | 3 / 47 (6.38%) | 10 / 218 (4.59%) |
| occurrences (all)                         | 3              | 3              | 10               |
| Hyperlipidaemia                           |                |                |                  |
| subjects affected / exposed               | 2 / 64 (3.13%) | 0 / 47 (0.00%) | 2 / 218 (0.92%)  |
| occurrences (all)                         | 2              | 0              | 2                |
| Hypertriglyceridaemia                     |                |                |                  |
| subjects affected / exposed               | 1 / 64 (1.56%) | 3 / 47 (6.38%) | 4 / 218 (1.83%)  |
| occurrences (all)                         | 1              | 3              | 4                |
| Dyslipidaemia                             |                |                |                  |
| subjects affected / exposed               | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 5 / 218 (2.29%)  |
| occurrences (all)                         | 1              | 0              | 5                |
| Dehydration                               |                |                |                  |
| subjects affected / exposed               | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 0 / 218 (0.00%)  |
| occurrences (all)                         | 0              | 0              | 0                |
| Diabetes mellitus                         |                |                |                  |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 1              | 0              | 1               |
| Increased appetite          |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Gout                        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Hypoglycaemia               |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Hypokalaemia                |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |
| Vitamin D deficiency        |                |                |                 |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 47 (0.00%) | 1 / 218 (0.46%) |
| occurrences (all)           | 0              | 0              | 1               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 19 January 2012   | Updated baseline characteristics and secondary endpoints. |
| 03 February 2012  | Updated baseline characteristics and secondary endpoints. |
| 27 September 2012 | Clarified planned analysis.                               |

Notes:

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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.

|  |
|--|
| The study was terminated early by the sponsor due to a decision to modify the drug development plan. The early termination was not due to a safety signal or lack of efficacy. |
|--|

Notes: