



## Clinical trial results:

**An open phase I/IIa trial to investigate the maximum tolerated dose, safety, pharmacokinetics and efficacy of intravenous BI 6727 as monotherapy or in combination with subcutaneous cytarabine in patients with acute myeloid leukaemia**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2008-003617-27 |
| Trial protocol           | DE BE AT       |
| Global end of trial date | 23 April 2021  |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 22 April 2022 |
| First version publication date | 22 April 2022 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 1230.4 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00804856 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Boehringer Ingelheim   |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany,   |
| Public contact               | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |
| Scientific contact           | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |

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                       | 05 May 2021   |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 09 March 2012 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 23 April 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the maximum tolerated dose (MTD), safety, pharmacokinetics and efficacy of volasertib monotherapy and volasertib in combination with low dose cytarabine (LDAC) in patients with acute myeloid leukaemia (AML)

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 05 December 2008 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Austria: 2   |
| Country: Number of subjects enrolled | Belgium: 20  |
| Country: Number of subjects enrolled | Canada: 7    |
| Country: Number of subjects enrolled | Germany: 126 |
| Country: Number of subjects enrolled | France: 23   |
| Country: Number of subjects enrolled | Italy: 8     |
| Country: Number of subjects enrolled | Norway: 7    |
| Worldwide total number of subjects   | 193          |
| EEA total number of subjects         | 186          |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|  |     |
|--|-----|
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 18  |
| From 65 to 84 years                      | 169 |
| 85 years and over                        | 6   |

## Subject disposition

### Recruitment

Recruitment details:

Open-label, randomized, dose escalation study. In this trial 180 patients were entered and randomised. However 3 patients were entered but not treated in Phase I and 2 patients were not treated in Phase II. Thus total 175 patients were treated in this trial.

### Pre-assignment

Screening details:

Patients were assigned to two treatment schedules (A and B) in the phase I part of the trial (dose escalation phase to determine maximum tolerated dose (MTD)). In the phase IIa part of the trial (after MTD was determined), patients were randomised to two treatment schedules (A and C).

### Period 1

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

Blinding implementation details:

This trial was conducted according to an open-label design.

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Phase I Schedule A. Volasertib 150 mg+LDAC |

Arm description:

Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Low-dose cytarabine (LDAC) |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Solution for injection     |
| Routes of administration               | Subcutaneous use           |

Dosage and administration details:

Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

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

Dosage and administration details:

Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |  |
|------------------|--|
| <b>Arm title</b> | Phase I Schedule A. Volasertib 200 mg+LDAC |
|------------------|--|

Arm description:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                            |
|--|----------------------------|
| Investigational medicinal product name | Low-dose cytarabine (LDAC) |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Solution for injection     |
| Routes of administration               | Subcutaneous use           |

Dosage and administration details:

Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

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

Dosage and administration details:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |  |
|------------------|--|
| <b>Arm title</b> | Phase I Schedule A. Volasertib 250 mg+LDAC |
|------------------|--|

Arm description:

Volasertib 250 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|  |                            |
|--|----------------------------|
| Investigational medicinal product name | Low-dose cytarabine (LDAC) |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Solution for injection     |
| Routes of administration               | Subcutaneous use           |

Dosage and administration details:

Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Phase I Schedule A. Volasertib 300 mg+LDAC |
|------------------|--|

Arm description:

Volasertib 300 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Volasertib 300 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|   |  |
|---|--|
| Investigational medicinal product name  | Low-dose cytarabine (LDAC)                 |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for injection                     |
| Routes of administration  | Subcutaneous use                           |
| Dosage and administration details:  |  |
| Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.  |  |
| <b>Arm title</b>  | Phase I Schedule A. Volasertib 350 mg+LDAC |
| Arm description:  |  |
| Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Arm type  | Experimental                               |
| Investigational medicinal product name  | Volasertib                                 |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for infusion                      |
| Routes of administration  | Intravenous use                            |
| Dosage and administration details:  |  |
| Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)   |  |
| Investigational medicinal product name  | Low-dose cytarabine (LDAC)                 |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for injection                     |
| Routes of administration  | Subcutaneous use                           |
| Dosage and administration details:  |  |
| Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.  |  |
| <b>Arm title</b>  | Phase I Schedule A. Volasertib 400 mg+LDAC |
| Arm description:  |  |
| Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Arm type  | Experimental                               |
| Investigational medicinal product name  | Volasertib                                 |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for infusion                      |
| Routes of administration  | Intravenous use                            |
| Dosage and administration details:  |  |
| Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)   |  |
| Investigational medicinal product name  | Low-dose cytarabine (LDAC)                 |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for injection                     |
| Routes of administration  | Subcutaneous use                           |
| Dosage and administration details:  |  |
| Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.  |  |
| <b>Arm title</b>  | Phase I Schedule B. Volasertib 150 mg      |

Arm description:

Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Phase I Schedule B. Volasertib 200 mg |
|------------------|---------------------------------------|

Arm description:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Phase I Schedule B. Volasertib 350 mg |
|------------------|---------------------------------------|

Arm description:

Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Phase I Schedule B. Volasertib 400 mg |
|------------------|---------------------------------------|

Arm description:

Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Phase I Schedule B. Volasertib 450 mg |
|------------------|---------------------------------------|

**Arm description:**

Volasertib 450 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Volasertib 450 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Phase I Schedule B. Volasertib 500 mg |
|------------------|---------------------------------------|

**Arm description:**

Volasertib 500 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Volasertib 500 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Phase I Schedule B. Volasertib 550 mg |
|------------------|---------------------------------------|

**Arm description:**

Volasertib 550 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Volasertib            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Volasertib 550 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Phase II Schedule C. LDAC |
|------------------|---------------------------|

**Arm description:**

Low-dose cytarabine (LDAC) monotherapy 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

|  |                            |
|--|----------------------------|
| Arm type                               | Active comparator          |
| Investigational medicinal product name | Low-dose cytarabine (LDAC) |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Solution for injection     |
| Routes of administration               | Subcutaneous use           |

**Dosage and administration details:**

Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Phase II Schedule A. Volasertib 350 mg+LDAC |
|------------------|---|



Arm description:

Volasertib 350 milligram (mg) on Days 1 and 15 (28-day cycle) administered by Intravenous Infusion (IV) over 60 minutes and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Low-dose cytarabine (LDAC) |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Solution for injection     |
| Routes of administration               | Subcutaneous use           |

Dosage and administration details:

Low-dose cytarabine (LDAC) 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

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

Dosage and administration details:

Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle)

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Phase I Schedule A. Volasertib 150 mg+LDAC | Phase I Schedule A. Volasertib 200 mg+LDAC | Phase I Schedule A. Volasertib 250 mg+LDAC |
|---|--|--|--|
| Started   | 4  | 3  | 5  |
| Completed   | 0  | 0  | 0  |
| Not completed                                       | 4  | 3  | 5  |
| Other Adverse Event                                 | 1  | 1  | 1  |
| Dose Limiting Toxicity (DLT)                        | -  | -  | -  |
| Progressive Disease                                 | 3  | 2  | 4  |
| Other reason than listed above                      | -  | -  | -  |
| Refused to continue medication                      | -  | -  | -  |
| Non compliance with protocol                        | -  | -  | -  |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Phase I Schedule A. Volasertib 300 mg+LDAC | Phase I Schedule A. Volasertib 350 mg+LDAC | Phase I Schedule A. Volasertib 400 mg+LDAC |
|---|--|--|--|
| Started   | 9  | 8  | 3  |
| Completed   | 0  | 0  | 0  |
| Not completed                                       | 9  | 8  | 3  |
| Other Adverse Event                                 | 2  | 2  | 1  |
| Dose Limiting Toxicity (DLT)                        | -  | 1  | -  |
| Progressive Disease                                 | 6  | 4  | 1  |
| Other reason than listed above                      | -  | -  | 1  |
| Refused to continue medication                      | 1  | 1  | -  |
| Non compliance with protocol                        | -  | -  | -  |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Phase I Schedule B. Volasertib 150 mg | Phase I Schedule B. Volasertib 200 mg | Phase I Schedule B. Volasertib 350 mg |
|---|---------------------------------------|---------------------------------------|---------------------------------------|
| Started   | 11                                    | 2                                     | 5                                     |
| Completed   | 0                                     | 0                                     | 0                                     |
| Not completed                                       | 11                                    | 2                                     | 5                                     |
| Other Adverse Event                                 | 3                                     | -                                     | -                                     |
| Dose Limiting Toxicity (DLT)                        | -                                     | -                                     | -                                     |
| Progressive Disease                                 | 8                                     | 2                                     | 4                                     |
| Other reason than listed above                      | -                                     | -                                     | 1                                     |
| Refused to continue medication                      | -                                     | -                                     | -                                     |
| Non compliance with protocol                        | -                                     | -                                     | -                                     |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Phase I Schedule B. Volasertib 400 mg | Phase I Schedule B. Volasertib 450 mg | Phase I Schedule B. Volasertib 500 mg |
|---|---------------------------------------|---------------------------------------|---------------------------------------|
| Started   | 6                                     | 23                                    | 5                                     |
| Completed   | 0                                     | 0                                     | 0                                     |
| Not completed                                       | 6                                     | 23                                    | 5                                     |
| Other Adverse Event                                 | 1                                     | 5                                     | 2                                     |
| Dose Limiting Toxicity (DLT)                        | -                                     | -                                     | -                                     |
| Progressive Disease                                 | 5                                     | 12                                    | 2                                     |
| Other reason than listed above                      | -                                     | 3                                     | 1                                     |
| Refused to continue medication                      | -                                     | 3                                     | -                                     |
| Non compliance with protocol                        | -                                     | -                                     | -                                     |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Phase I Schedule B. Volasertib 550 mg | Phase II Schedule C. LDAC | Phase II Schedule A. Volasertib 350 mg+LDAC |
|---|---------------------------------------|---------------------------|---|
| Started   | 4                                     | 45                        | 42  |
| Completed   | 0                                     | 0                         | 0   |
| Not completed                                       | 4                                     | 45                        | 42  |
| Other Adverse Event                                 | -                                     | 6                         | 13  |
| Dose Limiting Toxicity (DLT)                        | -                                     | -                         | 1   |
| Progressive Disease                                 | 2                                     | 26                        | 20  |
| Other reason than listed above                      | 1                                     | 10                        | 3   |
| Refused to continue medication                      | 1                                     | 1                         | 5   |
| Non compliance with protocol                        | -                                     | 2                         | -   |

Notes:

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

Justification: Out of the 193 enrolled subjects, 175 were treated and displayed here.

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Phase I Schedule A. Volasertib 150 mg+LDAC |
| Reporting group description:<br>Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 200 mg+LDAC |
| Reporting group description:<br>Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 250 mg+LDAC |
| Reporting group description:<br>Volasertib 250 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 300 mg+LDAC |
| Reporting group description:<br>Volasertib 300 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 350 mg+LDAC |
| Reporting group description:<br>Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 400 mg+LDAC |
| Reporting group description:<br>Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule B. Volasertib 150 mg      |
| Reporting group description:<br>Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 200 mg      |
| Reporting group description:<br>Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 350 mg      |
| Reporting group description:<br>Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 400 mg      |
| Reporting group description:<br>Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 450 mg      |
| Reporting group description:<br>Volasertib 450 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 500 mg      |
| Reporting group description:<br>Volasertib 500 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1   |  |

and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 550 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 550 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Phase II Schedule C. LDAC |
|-----------------------|---------------------------|

Reporting group description:

Low-dose cytarabine (LDAC) monotherapy 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

|                       |   |
|-----------------------|---|
| Reporting group title | Phase II Schedule A. Volasertib 350 mg+LDAC |
|-----------------------|---|

Reporting group description:

Volasertib 350 milligram (mg) on Days 1 and 15 (28-day cycle) administered by Intravenous Infusion (IV) over 60 minutes and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

| Reporting group values  | Phase I Schedule A. Volasertib 150 mg+LDAC | Phase I Schedule A. Volasertib 200 mg+LDAC | Phase I Schedule A. Volasertib 250 mg+LDAC |
|---|--|--|--|
| Number of subjects  | 4  | 3  | 5  |
| Age categorical   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: participants   |  |  |  |
| In utero  | 0  | 0  | 0  |
| Preterm newborn infants (gestational age < 37 wks)  | 0  | 0  | 0  |
| Newborns (0-27 days)  | 0  | 0  | 0  |
| Infants and toddlers (28 days-23 months)  | 0  | 0  | 0  |
| Children (2-11 years)   | 0  | 0  | 0  |
| Adolescents (12-17 years)   | 0  | 0  | 0  |
| Adults (18-64 years)  | 1  | 1  | 1  |
| From 65-84 years  | 3  | 2  | 4  |
| 85 years and over   | 0  | 0  | 0  |
| Age Continuous  |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: years  |  |  |  |
| arithmetic mean   | 69.5                                       | 67.0                                       | 71.2                                       |
| standard deviation  | ± 12.1                                     | ± 3.0                                      | ± 6.8                                      |
| Gender, Male/Female   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: Participants   |  |  |  |
| Female  | 2  | 0  | 2  |
| Male  | 2  | 3  | 3  |
| Race (NIH/OMB)  |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: Subjects   |  |  |  |
| American Indian or Alaska Native  | 0  | 0  | 0  |

|   |   |   |   |
|---|---|---|---|
| Asian                                     | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American                 | 0 | 0 | 0 |
| White                                     | 4 | 3 | 4 |
| More than one race                        | 0 | 0 | 0 |
| Unknown or Not Reported                   | 0 | 0 | 0 |

| <b>Reporting group values</b>   | Phase I Schedule A.<br>Volasertib 300<br>mg+LDAC | Phase I Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I Schedule A.<br>Volasertib 400<br>mg+LDAC |
|---|--|--|--|
| Number of subjects  | 9  | 8  | 3  |
| Age categorical   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: participants   |  |  |  |
| In utero  | 0  | 0  | 0  |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0  | 0  | 0  |
| Newborns (0-27 days)  | 0  | 0  | 0  |
| Infants and toddlers (28 days-23 months)  | 0  | 0  | 0  |
| Children (2-11 years)   | 0  | 0  | 0  |
| Adolescents (12-17 years)   | 0  | 0  | 0  |
| Adults (18-64 years)  | 2  | 1  | 0  |
| From 65-84 years  | 7  | 7  | 3  |
| 85 years and over   | 0  | 0  | 0  |
| Age Continuous  |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: years  |  |  |  |
| arithmetic mean   | 67.9   | 72.5   | 73.3   |
| standard deviation  | ± 12.0   | ± 6.1  | ± 7.6  |
| Gender, Male/Female   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: Participants   |  |  |  |
| Female  | 3  | 3  | 1  |
| Male  | 6  | 5  | 2  |
| Race (NIH/OMB)  |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: Subjects   |  |  |  |
| American Indian or Alaska Native  | 0  | 0  | 0  |
| Asian   | 1  | 0  | 0  |
| Native Hawaiian or Other Pacific Islander   | 0  | 0  | 0  |
| Black or African American   | 0  | 0  | 0  |
| White   | 8  | 8  | 3  |
| More than one race  | 0  | 0  | 0  |
| Unknown or Not Reported   | 0  | 0  | 0  |

| Reporting group values  | Phase I Schedule B.<br>Volasertib 150 mg | Phase I Schedule B.<br>Volasertib 200 mg | Phase I Schedule B.<br>Volasertib 350 mg |
|---|--|--|--|
| Number of subjects  | 11                                       | 2  | 5  |
| Age categorical   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: participants   |  |  |  |
| In utero  | 0  | 0  | 0  |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0  | 0  | 0  |
| Newborns (0-27 days)  | 0  | 0  | 0  |
| Infants and toddlers (28 days-23 months)  | 0  | 0  | 0  |
| Children (2-11 years)   | 0  | 0  | 0  |
| Adolescents (12-17 years)   | 0  | 0  | 0  |
| Adults (18-64 years)  | 0  | 0  | 0  |
| From 65-84 years  | 11                                       | 2  | 5  |
| 85 years and over   | 0  | 0  | 0  |
| Age Continuous  |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: years  |  |  |  |
| arithmetic mean   | 73.5                                     | 73.0                                     | 70.6                                     |
| standard deviation  | ± 3.9                                    | ± 4.2                                    | ± 2.9                                    |
| Gender, Male/Female   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: Participants   |  |  |  |
| Female  | 3  | 1  | 3  |
| Male  | 8  | 1  | 2  |
| Race (NIH/OMB)  |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: Subjects   |  |  |  |
| American Indian or Alaska Native  | 0  | 0  | 0  |
| Asian   | 0  | 0  | 0  |
| Native Hawaiian or Other Pacific Islander   | 0  | 0  | 0  |
| Black or African American   | 0  | 0  | 0  |
| White   | 11                                       | 2  | 5  |
| More than one race  | 0  | 0  | 0  |
| Unknown or Not Reported   | 0  | 0  | 0  |

| Reporting group values  | Phase I Schedule B.<br>Volasertib 400 mg | Phase I Schedule B.<br>Volasertib 450 mg | Phase I Schedule B.<br>Volasertib 500 mg |
|---|--|--|--|
| Number of subjects  | 6  | 23                                       | 5  |
| Age categorical   |  |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |  |  |  |
| Units: participants   |  |  |  |
| In utero  | 0  | 0  | 0  |

|   |        |       |       |
|---|--------|-------|-------|
| Preterm newborn infants (gestational age < 37 wks)  | 0      | 0     | 0     |
| Newborns (0-27 days)  | 0      | 0     | 0     |
| Infants and toddlers (28 days-23 months)  | 0      | 0     | 0     |
| Children (2-11 years)   | 0      | 0     | 0     |
| Adolescents (12-17 years)   | 0      | 0     | 0     |
| Adults (18-64 years)  | 1      | 7     | 1     |
| From 65-84 years  | 5      | 16    | 4     |
| 85 years and over   | 0      | 0     | 0     |
| Age Continuous  |        |       |       |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |        |       |       |
| Units: years  |        |       |       |
| arithmetic mean   | 65.2   | 68.2  | 66.4  |
| standard deviation  | ± 20.1 | ± 7.7 | ± 7.3 |
| Gender, Male/Female   |        |       |       |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |        |       |       |
| Units: Participants   |        |       |       |
| Female  | 2      | 16    | 1     |
| Male  | 4      | 7     | 4     |
| Race (NIH/OMB)  |        |       |       |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |        |       |       |
| Units: Subjects   |        |       |       |
| American Indian or Alaska Native  | 0      | 0     | 0     |
| Asian   | 0      | 0     | 0     |
| Native Hawaiian or Other Pacific Islander   | 0      | 0     | 0     |
| Black or African American   | 0      | 0     | 0     |
| White   | 6      | 21    | 5     |
| More than one race  | 0      | 0     | 0     |
| Unknown or Not Reported   | 0      | 2     | 0     |

| Reporting group values  | Phase I Schedule B. Volasertib 550 mg | Phase II Schedule C. LDAC | Phase II Schedule A. Volasertib 350 mg+LDAC |
|---|---------------------------------------|---------------------------|---|
| Number of subjects  | 4                                     | 45                        | 42  |
| Age categorical   |                                       |                           |   |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |                                       |                           |   |
| Units: participants   |                                       |                           |   |
| In utero  | 0                                     | 0                         | 0   |
| Preterm newborn infants (gestational age < 37 wks)  | 0                                     | 0                         | 0   |
| Newborns (0-27 days)  | 0                                     | 0                         | 0   |
| Infants and toddlers (28 days-23 months)  | 0                                     | 0                         | 0   |
| Children (2-11 years)   | 0                                     | 0                         | 0   |
| Adolescents (12-17 years)   | 0                                     | 0                         | 0   |
| Adults (18-64 years)  | 0                                     | 2                         | 0   |

|                   |   |    |    |
|-------------------|---|----|----|
| From 65-84 years  | 4 | 41 | 40 |
| 85 years and over | 0 | 2  | 2  |

|   |       |       |       |
|---|-------|-------|-------|
| Age Continuous  |       |       |       |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |       |       |       |
| Units: years  |       |       |       |
| arithmetic mean   | 69.8  | 75.2  | 75.6  |
| standard deviation  | ± 4.1 | ± 5.5 | ± 4.9 |
| Gender, Male/Female   |       |       |       |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |       |       |       |
| Units: Participants   |       |       |       |
| Female  | 3     | 20    | 19    |
| Male  | 1     | 25    | 23    |
| Race (NIH/OMB)  |       |       |       |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |       |       |       |
| Units: Subjects   |       |       |       |
| American Indian or Alaska Native  | 0     | 1     | 0     |
| Asian   | 0     | 1     | 1     |
| Native Hawaiian or Other Pacific Islander   | 0     | 0     | 0     |
| Black or African American   | 0     | 0     | 0     |
| White   | 4     | 35    | 34    |
| More than one race  | 0     | 0     | 0     |
| Unknown or Not Reported   | 0     | 8     | 7     |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 175   |  |  |
| Age categorical   |       |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |       |  |  |
| Units: participants   |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks)  | 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)  | 17    |  |  |
| From 65-84 years  | 154   |  |  |
| 85 years and over   | 4     |  |  |
| Age Continuous  |       |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |       |  |  |
| Units: years  |       |  |  |
| arithmetic mean   |       |  |  |



|                    |   |  |  |
|--------------------|---|--|--|
| standard deviation | - |  |  |
|--------------------|---|--|--|

|   |     |  |  |
|---|-----|--|--|
| Gender, Male/Female   |     |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |     |  |  |
| Units: Participants   |     |  |  |
| Female  | 79  |  |  |
| Male  | 96  |  |  |
| Race (NIH/OMB)  |     |  |  |
| Treated Set: All patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. For the Phase II part, the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC. |     |  |  |
| Units: Subjects   |     |  |  |
| American Indian or Alaska Native  | 1   |  |  |
| Asian   | 4   |  |  |
| Native Hawaiian or Other Pacific Islander   | 0   |  |  |
| Black or African American   | 0   |  |  |
| White   | 153 |  |  |
| More than one race  | 0   |  |  |
| Unknown or Not Reported   | 17  |  |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Phase I Schedule A. Volasertib 150 mg+LDAC |
| Reporting group description:<br>Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 200 mg+LDAC |
| Reporting group description:<br>Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 250 mg+LDAC |
| Reporting group description:<br>Volasertib 250 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 300 mg+LDAC |
| Reporting group description:<br>Volasertib 300 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 350 mg+LDAC |
| Reporting group description:<br>Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule A. Volasertib 400 mg+LDAC |
| Reporting group description:<br>Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. |  |
| Reporting group title   | Phase I Schedule B. Volasertib 150 mg      |
| Reporting group description:<br>Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 200 mg      |
| Reporting group description:<br>Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 350 mg      |
| Reporting group description:<br>Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 400 mg      |
| Reporting group description:<br>Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 450 mg      |
| Reporting group description:<br>Volasertib 450 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).  |  |
| Reporting group title   | Phase I Schedule B. Volasertib 500 mg      |
| Reporting group description:<br>Volasertib 500 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1   |  |

and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 550 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 550 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Phase II Schedule C. LDAC |
|-----------------------|---------------------------|

Reporting group description:

Low-dose cytarabine (LDAC) monotherapy 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

|                       |   |
|-----------------------|---|
| Reporting group title | Phase II Schedule A. Volasertib 350 mg+LDAC |
|-----------------------|---|

Reporting group description:

Volasertib 350 milligram (mg) on Days 1 and 15 (28-day cycle) administered by Intravenous Infusion (IV) over 60 minutes and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Phase I Schedule A. Volasertib+LDAC |
|----------------------------|-------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

PVolasertib escalating dose on Days 1 and 15 (28-day cycle). Dose escalation in 50 milligram (mg) steps up to 400 mg, with a starting dose of 150 mg and LDAC 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle until the patient met criteria for stopping study medication during the MTD evaluation period.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Phase I Schedule B. Volasertib |
|----------------------------|--------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Volasertib escalating dose on Days 1 and 15 (28-day cycle). Dose escalation in 50 milligram (mg) steps from an initial starting dose of 150 mg; dose escalation stopped at 200 mg and then restarted from the MTD dose in Schedule A (350 mg); dose was escalated up to 550 mg. Volasertib administered by Intravenous Infusion (IV) over 60 minutes.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Phase II Combined. Schedule A and C |
|----------------------------|-------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Volasertib escalating dose on Days 1 and 15 (28-day cycle). Dose escalation in 50 milligram (mg) steps up to 400 mg, with a starting dose of 150 mg. Volasertib 350 mg on Days 1+15 (28-day cycle) administered by Intravenous Infusion (IV) over 60 minutes and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Dose norm Volasertib+LDAC (Phase I A). 150-400 mg Volasertib |
|----------------------------|--|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Volasertib 150 to 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle. Dose groups of Phase I were combined by dose normalizing as pre specified in the study protocol.

|                            |                                   |
|----------------------------|-----------------------------------|
| Subject analysis set title | Phase I+II Volasertib 350 mg+LDAC |
|----------------------------|-----------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Phase I+II: Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

### **Primary: Phase I: Maximum Tolerated Dose (MTD) of Volasertib in Combination with LDAC (schedule A) and Volasertib monotherapy (schedule B)**

|                 |  |
|-----------------|--|
| End point title | Phase I: Maximum Tolerated Dose (MTD) of Volasertib in Combination with LDAC (schedule A) and Volasertib monotherapy (schedule B) <sup>[1]</sup> |
|-----------------|--|

End point description:

To determine the Maximum tolerated dose (MTD), dose escalation was conducted following 3+3 design with de-escalation. The MTD was defined as the highest dose at which 6 patients had been treated and less than 2 patients experienced a Dose limiting toxicity (DLT), first cycle only. DLT is defined as drug

related Common terminology criteria for adverse events (CTCAE) grade  $\geq 3$  nonhaematological toxicity (excluding: untreated nausea, untreated vomiting, CTCAE grade 3 untreated diarrhoea, CTCAE grade 3 "febrile neutropenia" and CTCAE grade 3 "infection with grade 3 or 4 neutrophils"). In patients with CRi or PR, persistent CTCAE grade 4 neutropenia or thrombocytopenia until three weeks after the end of the treatment cycle were regarded a DLT. Treated Set-phase I part: all patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason.

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

End point timeframe:

First Treatment cycle, up to 28 days.

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: As pre-specified in the protocol this end point only analyses the Phase I arms.

| End point values            | Phase I<br>Schedule A.<br>Volasertib+LDAC | Phase I<br>Schedule B.<br>Volasertib |  |  |
|-----------------------------|---|--------------------------------------|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                 |  |  |
| Number of subjects analysed | 32  | 56                                   |  |  |
| Units: milligram (mg)       | 350                                       | 450                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Phase II: Number of patients with Objective Response (Complete remission (CR) + Complete remission with incomplete blood count recovery (CRi))

|                 |   |
|-----------------|---|
| End point title | Phase II: Number of patients with Objective Response (Complete remission (CR) + Complete remission with incomplete blood count recovery (CRi)) <sup>[2]</sup> |
|-----------------|---|

End point description:

Phase II: Number of patients with Objective Response (Complete remission (CR) + Complete remission with incomplete blood count recovery (CRi)).

Treated set-phase II part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.

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

End point timeframe:

The best overall response recorded during the time period from the start of the treatment until end of the treatment period, progression or death (whichever was earlier), up to 869 days.

Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase II arms.

| End point values            | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type          | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed | 45                              | 42   |  |  |
| Units: Participants         | 6                               | 13   |  |  |

## Statistical analyses

| Statistical analysis title  | Statistical Analysis  |
|---|---|
| Statistical analysis description:   |   |
| Analysis for Objective Response. Ratio calculated as Phase II Schedule A Volasertib 350mg+LDAC divided by Phase II Schedule C LDAC. |   |
| Comparison groups   | Phase II Schedule C. LDAC v Phase II Schedule A. Volasertib 350 mg+LDAC |
| Number of subjects included in analysis   | 87  |
| Analysis specification  | Pre-specified   |
| Analysis type   |   |
| P-value   | = 0.0523  |
| Method  | Regression, Logistic  |
| Parameter estimate  | Odds ratio (OR)   |
| Point estimate  | 2.91  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.99  |
| upper limit   | 8.58  |

## Primary: Phase I: Number of Participants with Dose Limiting Toxicities (DLTs) in the First Cycle for the Determination of the Maximum Tolerated Dose (MTD)

|                 |   |
|-----------------|---|
| End point title | Phase I: Number of Participants with Dose Limiting Toxicities (DLTs) in the First Cycle for the Determination of the Maximum Tolerated Dose (MTD) <sup>[3][4]</sup> |
|-----------------|---|

### End point description:

A DLT was defined as a drug related CTCAE (Common Toxicity Criteria for Adverse Events) Grade  $\geq 3$  non-haematological toxicity (excluding untreated nausea, untreated vomiting, Grade 3 untreated diarrhea, Grade 3 febrile neutropenia, and Grade 3 infection with Grade 3 or 4 neutrophils). In patients with CRi (Complete Remission with Incomplete Blood Count Recovery) or PR (Partial Remission), persistent Grade 4 neutropenia or thrombocytopenia for 3 weeks after the end of the treatment cycle was regarded as a DLT unless the respective Grade 4 cytopenia was preexistent. In patients who required platelet substitution to maintain a Grade  $<4$  before treatment, a Grade 4 thrombocytopenia after treatment did not constitute a DLT.

Treated Set-Phase I part: Treated Set was defined as all patients who received at least a single dose of either Volasertib (BI 6727) or LDAC (Low-Dose Cytarabine), including patients who were replaced for any reason.

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

### End point timeframe:

First Treatment cycle, up to 28 days.

### Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase I arms.

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

Justification: As pre-specified in the protocol this end point only analyses the Phase I arms.

| End point values            | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|-----------------------------|---|---|---|---|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed | 4   | 3   | 5   | 9   |
| Units: Participants         | 0   | 0   | 0   | 1   |

| End point values            | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule B.<br>Volasertib 150<br>mg | Phase I<br>Schedule B.<br>Volasertib 200<br>mg |
|-----------------------------|---|---|--|--|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 8   | 3   | 11   | 2  |
| Units: Participants         | 1   | 2   | 1  | 0  |

| End point values            | Phase I<br>Schedule B.<br>Volasertib 350<br>mg | Phase I<br>Schedule B.<br>Volasertib 400<br>mg | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I<br>Schedule B.<br>Volasertib 500<br>mg |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                                | Reporting group                                | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 5  | 6  | 23   | 5  |
| Units: Participants         | 0  | 1  | 1  | 2  |

| End point values            | Phase I<br>Schedule B.<br>Volasertib 550<br>mg | Phase I<br>Schedule A.<br>Volasertib+LDA<br>C | Phase I<br>Schedule B.<br>Volasertib |  |
|-----------------------------|--|---|--------------------------------------|--|
| Subject group type          | Reporting group                                | Subject analysis set                          | Subject analysis set                 |  |
| Number of subjects analysed | 4  | 32  | 56                                   |  |
| Units: Participants         | 2  | 4   | 7                                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response

|                 |                       |
|-----------------|-----------------------|
| End point title | Best Overall Response |
|-----------------|-----------------------|

End point description:

Best overall response: The best overall response recorded during the time period from the start of the treatment until end of the treatment period, progression or death (whichever was earlier). Possible responses for best overall response were: Complete remission (CR), Complete remission with incomplete blood count recovery (CRi), Partial remission (PR), no change, aplasia, Indeterminate, Progressive disease (PD), Not evaluable or missing. Patients dying before any assessment were classified as PD for best overall response. The number of participants for each response is reported.

Treated Set-phase I part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. Phase II part, the

Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.

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

End point timeframe:

The best overall response recorded during the time period from the start of the treatment until end of the treatment period, progression or death (whichever was earlier), up to 869 days.

| End point values            | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|-----------------------------|---|---|---|---|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed | 4   | 3   | 5   | 9   |
| Units: Participants         |   |   |   |   |
| Complete remission          | 0   | 0   | 2   | 0   |
| CRi                         | 0   | 2   | 0   | 1   |
| Partial remission           | 0   | 0   | 0   | 0   |
| No change                   | 2   | 1   | 2   | 1   |
| Aplasia                     | 0   | 0   | 0   | 0   |
| Indeterminate               | 0   | 0   | 0   | 2   |
| Progressive disease         | 2   | 0   | 1   | 3   |
| Not evaluable               | 0   | 0   | 0   | 1   |
| Missing                     | 0   | 0   | 0   | 1   |

| End point values            | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule B.<br>Volasertib 150<br>mg | Phase I<br>Schedule B.<br>Volasertib 200<br>mg |
|-----------------------------|---|---|--|--|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 8   | 3   | 11   | 2  |
| Units: Participants         |   |   |  |  |
| Complete remission          | 0   | 0   | 0  | 0  |
| CRi                         | 1   | 0   | 0  | 0  |
| Partial remission           | 0   | 0   | 0  | 0  |
| No change                   | 1   | 1   | 4  | 0  |
| Aplasia                     | 0   | 0   | 0  | 0  |
| Indeterminate               | 3   | 1   | 1  | 0  |
| Progressive disease         | 3   | 1   | 6  | 2  |
| Not evaluable               | 0   | 0   | 0  | 0  |
| Missing                     | 0   | 0   | 0  | 0  |

| End point values            | Phase I<br>Schedule B.<br>Volasertib 350<br>mg | Phase I<br>Schedule B.<br>Volasertib 400<br>mg | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I<br>Schedule B.<br>Volasertib 500<br>mg |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                                | Reporting group                                | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 5  | 6  | 23   | 5  |
| Units: Participants         |  |  |  |  |

|                     |   |   |   |   |
|---------------------|---|---|---|---|
| Complete remission  | 0 | 0 | 0 | 0 |
| CRi                 | 1 | 2 | 2 | 0 |
| Partial remission   | 1 | 0 | 2 | 0 |
| No change           | 2 | 2 | 7 | 3 |
| Aplasia             | 0 | 1 | 3 | 1 |
| Indeterminate       | 0 | 0 | 0 | 0 |
| Progressive disease | 1 | 1 | 7 | 1 |
| Not evaluable       | 0 | 0 | 2 | 0 |
| Missing             | 0 | 0 | 0 | 0 |

| <b>End point values</b>     | Phase I<br>Schedule B.<br>Volasertib 550<br>mg | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib+LDA<br>C |
|-----------------------------|--|---------------------------------|--|---|
| Subject group type          | Reporting group                                | Reporting group                 | Reporting group                                      | Subject analysis set                          |
| Number of subjects analysed | 4  | 45                              | 42   | 32  |
| Units: Participants         |  |                                 |  |   |
| Complete remission          | 0  | 3                               | 6  | 2   |
| CRi                         | 0  | 3                               | 7  | 4   |
| Partial remission           | 1  | 2                               | 2  | 0   |
| No change                   | 0  | 18                              | 15   | 8   |
| Aplasia                     | 1  | 0                               | 0  | 0   |
| Indeterminate               | 0  | 3                               | 5  | 6   |
| Progressive disease         | 1  | 14                              | 7  | 10  |
| Not evaluable               | 1  | 2                               | 0  | 1   |
| Missing                     | 0  | 0                               | 0  | 1   |

| <b>End point values</b>     | Phase I<br>Schedule B.<br>Volasertib | Phase II<br>Combined.<br>Schedule A and<br>C |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Subject analysis set                 | Subject analysis set                         |  |  |
| Number of subjects analysed | 56                                   | 87   |  |  |
| Units: Participants         |                                      |  |  |  |
| Complete remission          | 0                                    | 9  |  |  |
| CRi                         | 5                                    | 10   |  |  |
| Partial remission           | 4                                    | 4  |  |  |
| No change                   | 18                                   | 33   |  |  |
| Aplasia                     | 6                                    | 0  |  |  |
| Indeterminate               | 1                                    | 8  |  |  |
| Progressive disease         | 19                                   | 21   |  |  |
| Not evaluable               | 3                                    | 2  |  |  |
| Missing                     | 0                                    | 0  |  |  |

## Statistical analyses



**Secondary: Phase I: Number of Patients with Objective Response: Complete remission or Complete remission with incomplete blood count recovery (CR+CRi)**

|                 |  |
|-----------------|--|
| End point title | Phase I: Number of Patients with Objective Response: Complete remission or Complete remission with incomplete blood count recovery (CR+CRi) <sup>[5]</sup> |
|-----------------|--|

## End point description:

Phase I: Objective Response (yes/no): yes=Best Overall Response of Complete remission (CR) or Complete remission with incomplete blood count recovery (CRi), no=all others.  
Treated Set-phase I part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason.

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

## End point timeframe:

The best overall response recorded during the time period from the start of the treatment until end of the treatment period, progression or death (whichever was earlier), up to 594 days.

## Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase I arms.

| End point values            | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|-----------------------------|---|---|---|---|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed | 4   | 3   | 5   | 9   |
| Units: Participants         | 0   | 2   | 2   | 1   |

| End point values            | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule B.<br>Volasertib 150<br>mg | Phase I<br>Schedule B.<br>Volasertib 200<br>mg |
|-----------------------------|---|---|--|--|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 8   | 3   | 11   | 2  |
| Units: Participants         | 1   | 0   | 0  | 0  |

| End point values            | Phase I<br>Schedule B.<br>Volasertib 350<br>mg | Phase I<br>Schedule B.<br>Volasertib 400<br>mg | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I<br>Schedule B.<br>Volasertib 500<br>mg |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                                | Reporting group                                | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 5  | 6  | 23   | 5  |
| Units: Participants         | 1  | 2  | 2  | 0  |

| End point values | Phase I<br>Schedule B.<br>Volasertib 550<br>mg | Phase I<br>Schedule A.<br>Volasertib+LDA<br>C | Phase I<br>Schedule B.<br>Volasertib |  |
|------------------|--|---|--------------------------------------|--|
|------------------|--|---|--------------------------------------|--|

|                             |                 |                      |                      |  |
|-----------------------------|-----------------|----------------------|----------------------|--|
| Subject group type          | Reporting group | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed | 4               | 32                   | 56                   |  |
| Units: Participants         | 0               | 6                    | 5                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Event Free Survival

|                 |  |
|-----------------|--|
| End point title | Phase II: Event Free Survival <sup>[6]</sup> |
|-----------------|--|

End point description:

Event-free survival (EFS) [days] was the shortest duration of the following: (a) Date of assessment indicating PD on the response page of the eCRF (Electronic Case Report Form) – date of randomisation + 1 day (b) Date of assessment indicating clinical progressive disease (PD) on the disease or responses pages of the of eCRF– date of randomisation + 1 day (c) Date of assessment indicating PD on the patient status page of the eCRF – date of randomisation +1 day (for patients who had not been censored before this time point) (d) Death date – date of randomisation +1 day. Patients not being assessed PD, clinical PD, or death during the trial were censored. EFS was analysed with the Kaplan-Meier method for each of the treatment arms.

Treated Set-Phase II part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.

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

End point timeframe:

The patients that entered the trial, and measured from the date of randomization to the date of disease progression (treatment failure), relapse or death from any cause, whichever occurred first, up to 1000 days..

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As pre-specified in the protocol this end point only analyses the Phase II arms.

| End point values                      | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|---------------------------------------|---------------------------------|--|--|--|
| Subject group type                    | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed           | 45                              | 42   |  |  |
| Units: Days                           |                                 |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 69.0 (27 to 215)                | 169.0 (39 to 470)                                    |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

An exploratory (non-stratified) logrank test was used to compare the different treatment arms.

|                   |   |
|-------------------|---|
| Comparison groups | Phase II Schedule C. LDAC v Phase II Schedule A. Volasertib 350 mg+LDAC |
|-------------------|---|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 87                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           |                   |
| P-value                                 | = 0.0208          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.57              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.35              |
| upper limit                             | 0.92              |

## Secondary: Phase II: Overall Survival

|   |   |
|---|---|
| End point title   | Phase II: Overall Survival <sup>[7]</sup> |
| End point description:  |   |
| Overall survival [days] = (date of death - date of randomisation + 1 day), for patients with known date of death. Overall survival (censored) [days] = (date of last trial visit or follow-up - date of randomisation + 1 day), for patients who were still alive at time of database lock. |   |
| Overall survival (OS) was analysed with the Kaplan-Meier method for each of the treatment arms.   |   |
| Treated Set-Phase II part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.  |   |
| End point type  | Secondary                                 |
| End point timeframe:  |   |
| The patients that entered the trial, and measured from the date of randomisation until death from any cause, up to 1100 days..  |   |

Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase II arms.

| End point values                      | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|---------------------------------------|---------------------------------|--|--|--|
| Subject group type                    | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed           | 45                              | 42   |  |  |
| Units: Days                           |                                 |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 158.0 (78 to 347)               | 245.0 (73 to 689)                                    |  |  |

## Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Statistical analysis 3  |
| Statistical analysis description:  |   |
| An exploratory (non-stratified) logrank test was used to compare the different treatment arms. |   |
| Comparison groups  | Phase II Schedule C. LDAC v Phase II Schedule A. Volasertib 350 mg+LDAC |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 87                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           |                   |
| P-value                                 | = 0.0465          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.63              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.4               |
| upper limit                             | 1                 |

## Secondary: Phase II: Relapse - Free Survival

|                 |  |
|-----------------|--|
| End point title | Phase II: Relapse - Free Survival <sup>[8]</sup> |
|-----------------|--|

End point description:

Relapse-free survival [days] = (date of first recurrence of disease or death after entering the trial – date of first occurrence of CR or CRi after entering the trial+ 1 day) for patients with a recurrence (this value should be positive).

Relapse-free survival (censored) [days] = (date of last trial visit or follow-up - date of first occurrence of CR or CRi after entering the trial + 1 day) for patients who did not experience recurrence of disease or death at the time of analysis.

Patients in Treated Set-Phase II with objective response. Treated Set-Phase II part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.

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

End point timeframe:

The patients who achieved CR or CRi, and was measured from the date of attaining CR or CRi until the date of disease recurrence or death from any cause, whichever occurred first, up to 900 days.

Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase II arms.

| End point values                      | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|---------------------------------------|---------------------------------|--|--|--|
| Subject group type                    | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed           | 6                               | 13 <sup>[9]</sup>                                    |  |  |
| Units: Days                           |                                 |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 304.0 (113 to 367)              | 563.0 (427 to 99999)                                 |  |  |

Notes:

[9] - 99999 = NA, 25% quartile not reached, not enough events occurred.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase II: Remission Duration

|                 |  |
|-----------------|--|
| End point title | Phase II: Remission Duration <sup>[10]</sup> |
|-----------------|--|

**End point description:**

Remission duration analysis was defined only for patients who achieved Complete remission (CR) or Complete remission with incomplete blood count recovery (CRi), and was measured from the date of attaining CR or CRi until the date of disease recurrence (relapse). For patients who died without report of relapse, remission duration was censored on the date of death, regardless of cause.

Patients in Treated Set-Phase II with objective response. Treated Set-Phase II part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.

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

**End point timeframe:**

The patients who achieved CR or CRi, and was measured from the date of attaining CR or CRi until the date of disease recurrence (relapse), up to 900 days.

**Notes:**

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

Justification: As pre-specified in the protocol this end point only analyses the Phase II arms.

| End point values                      | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|---------------------------------------|---------------------------------|--|--|--|
| Subject group type                    | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed           | 6                               | 13 <sup>[11]</sup>                                   |  |  |
| Units: Days                           |                                 |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 367.0 (113 to 367)              | 687.0 (427 to 99999)                                 |  |  |

**Notes:**

[11] - 99999 = NA, 25% quartile not reached, not enough events occurred.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Phase II: Time to Remission**

|                 |   |
|-----------------|---|
| End point title | Phase II: Time to Remission <sup>[12]</sup> |
|-----------------|---|

**End point description:**

Time to remission [days] = (date of first occurrence of CR or CRi after entering the trial–date of randomisation + 1 day) for patients with an objective response.

Patients in Treated Set-Phase II with objective response. Treated Set-Phase II part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC.

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

**End point timeframe:**

The patients who achieved CR or CRi, and was measured from the date of attaining CR or CRi until the date of disease recurrence (relapse), up to 158 days.

**Notes:**

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

Justification: As pre-specified in the protocol this end point only analyses the Phase II arms.

| End point values            | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type          | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed | 6                               | 13   |  |  |
| Units: Days                 |                                 |  |  |  |

|                               |                  |                  |  |  |
|-------------------------------|------------------|------------------|--|--|
| median (full range (min-max)) | 63.5 (30 to 125) | 71.0 (29 to 158) |  |  |
|-------------------------------|------------------|------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Eastern Co-operative Oncology Group (ECOG) Performance Score from Baseline until End of Treatment

|                 |  |
|-----------------|--|
| End point title | Best Eastern Co-operative Oncology Group (ECOG) Performance Score from Baseline until End of Treatment |
|-----------------|--|

End point description:

ECOG performance score change from baseline to last visit of last cycle = ECOG performance score at last visit of the last cycle – ECOG performance score at baseline. ECOG performance score changes from baseline were also categorised on a 3-point categorical scale: deteriorated (-1), unchanged (0), and improved (1). The number of participants for category of ECOG score change is reported.

Treated Set-Phase I part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. Phase II part, the Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC. Only participants with non-missing values are reported.

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

End point timeframe:

Baseline and End of Treatment (up to 869 days).

| End point values            | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|-----------------------------|---|---|---|---|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed | 4   | 3   | 5   | 5   |
| Units: Participants         |   |   |   |   |
| Unchanged                   | 3   | 1   | 5   | 2   |
| Improved                    | 0   | 2   | 0   | 1   |
| Deteriorated                | 1   | 0   | 0   | 2   |

| End point values            | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule B.<br>Volasertib 150<br>mg | Phase I<br>Schedule B.<br>Volasertib 200<br>mg |
|-----------------------------|---|---|--|--|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 8   | 2   | 10   | 2  |
| Units: Participants         |   |   |  |  |
| Unchanged                   | 5   | 1   | 9  | 1  |
| Improved                    | 0   | 0   | 0  | 0  |
| Deteriorated                | 3   | 1   | 1  | 1  |

| End point values            | Phase I<br>Schedule B.<br>Volasertib 350<br>mg | Phase I<br>Schedule B.<br>Volasertib 400<br>mg | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I<br>Schedule B.<br>Volasertib 500<br>mg |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                                | Reporting group                                | Reporting group                                | Reporting group                                |
| Number of subjects analysed | 5  | 6  | 22   | 5  |
| Units: Participants         |  |  |  |  |
| Unchanged                   | 0  | 4  | 14   | 2  |
| Improved                    | 1  | 1  | 3  | 1  |
| Deteriorated                | 4  | 1  | 5  | 2  |

| End point values            | Phase I<br>Schedule B.<br>Volasertib 550<br>mg | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib+LDA<br>C |
|-----------------------------|--|---------------------------------|--|---|
| Subject group type          | Reporting group                                | Reporting group                 | Reporting group                                      | Subject analysis set                          |
| Number of subjects analysed | 3  | 42                              | 39   | 27  |
| Units: Participants         |  |                                 |  |   |
| Unchanged                   | 3  | 22                              | 15   | 17  |
| Improved                    | 0  | 8                               | 13   | 3   |
| Deteriorated                | 0  | 12                              | 11   | 7   |

| End point values            | Phase I<br>Schedule B.<br>Volasertib | Phase II<br>Combined.<br>Schedule A and<br>C |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Subject analysis set                 | Subject analysis set                         |  |  |
| Number of subjects analysed | 53                                   | 81   |  |  |
| Units: Participants         |                                      |  |  |  |
| Unchanged                   | 33                                   | 37   |  |  |
| Improved                    | 6                                    | 21   |  |  |
| Deteriorated                | 14                                   | 23   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total Clearance (CL) of Volasertib in Plasma after i.v (Intravenous) Administration of Volasertib

|                 |   |
|-----------------|---|
| End point title | Total Clearance (CL) of Volasertib in Plasma after i.v (Intravenous) Administration of Volasertib <sup>[13]</sup> |
|-----------------|---|

End point description:

Total Clearance (CL) of Volasertib in Plasma after Intravenous (i.v.) Administration of Volasertib. Pharmacokinetic (PK) set which included all patients in the treated set who had at least 1 evaluable

blood sample during cycle 1. Phase I Schedule B Volasertib 200mg+LDAC was not analysed as there was insufficient data, Only participants with non-missing values are reported.

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

End point timeframe:

Cycle 1: -0:05 hour (h), 0:30h, 1:00h, 1:30h, 2h, 3h, 4h, 24h, 96h, 216h, 335:55h, 336:30h, 337h, 337:30h, 338h, 339h, 340h, 648h after first drug administration.

Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase I and Phase IIA arms.

| End point values                                    | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|---|---|---|---|---|
| Subject group type                                  | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed                         | 4   | 3   | 5   | 8   |
| Units: millilitre/minute (mL/min)                   |   |   |   |   |
| geometric mean (geometric coefficient of variation) | 1280 ( $\pm$ 52.8)                                  | 972 ( $\pm$ 26.6)                                   | 864 ( $\pm$ 27.6)                                   | 1150 ( $\pm$ 34.4)                                  |

| End point values                                    | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule B.<br>Volasertib 150<br>mg | Phase I<br>Schedule B.<br>Volasertib 200<br>mg |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                                     | Reporting group                                     | Reporting group                                | Reporting group                                |
| Number of subjects analysed                         | 8   | 3   | 10   | 1 <sup>[14]</sup>                              |
| Units: millilitre/minute (mL/min)                   |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 1000 ( $\pm$ 36.2)                                  | 852 ( $\pm$ 49.6)                                   | 1330 ( $\pm$ 29.3)                             | 9999 ( $\pm$ 9999)                             |

Notes:

[14] - 9999 = not calculable with one subject

| End point values                                    | Phase I<br>Schedule B.<br>Volasertib 350<br>mg | Phase I<br>Schedule B.<br>Volasertib 400<br>mg | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I<br>Schedule B.<br>Volasertib 500<br>mg |
|---|--|--|--|--|
| Subject group type                                  | Reporting group                                | Reporting group                                | Reporting group                                | Reporting group                                |
| Number of subjects analysed                         | 5  | 6  | 22   | 5  |
| Units: millilitre/minute (mL/min)                   |  |  |  |  |
| geometric mean (geometric coefficient of variation) | 810 ( $\pm$ 35.1)                              | 1120 ( $\pm$ 62.1)                             | 920 ( $\pm$ 36.2)                              | 1140 ( $\pm$ 38.5)                             |

| End point values                  | Phase I<br>Schedule B.<br>Volasertib 550<br>mg | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                | Reporting group                                      |  |  |
| Number of subjects analysed       | 3  | 31   |  |  |
| Units: millilitre/minute (mL/min) |  |  |  |  |



|   |                   |                   |  |  |
|---|-------------------|-------------------|--|--|
| geometric mean (geometric coefficient of variation) | 939 ( $\pm$ 93.2) | 897 ( $\pm$ 42.8) |  |  |
|---|-------------------|-------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Apparent Volume of Distribution of volasertib at steady state (VSS)

|                 |   |
|-----------------|---|
| End point title | Apparent Volume of Distribution of volasertib at steady state (VSS) <sup>[15]</sup> |
|-----------------|---|

End point description:

Apparent Volume of Distribution of volasertib at steady state (VSS) following Intravenous (i.v.) administration.

Pharmacokinetic (PK) set which included all patients in the treated set who had at least 1 evaluable blood sample during cycle 1. Phase I Schedule B Volasertib 200mg+LDAC was not analysed as there was insufficient data.

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

End point timeframe:

Cycle 1: -0:05 hour (h), 0:30h, 1:00h, 1:30h, 2h, 3h, 4h, 24h, 96h, 216h, 335:55h, 336:30h, 337h, 337:30h, 338h, 339h, 340h, 648h after first drug administration.

Notes:

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

Justification: As pre-specified in the protocol this end point only analyses the Phase I and Phase IIA arms.

| End point values                                    | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|---|---|---|---|---|
| Subject group type                                  | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed                         | 4   | 3   | 5   | 8   |
| Units: Liter (L)                                    |   |   |   |   |
| geometric mean (geometric coefficient of variation) | 10600 ( $\pm$ 111.0)                                | 8640 ( $\pm$ 14.1)                                  | 7000 ( $\pm$ 26.6)                                  | 6320 ( $\pm$ 35.9)                                  |

| End point values                                    | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule B.<br>Volasertib 150<br>mg | Phase I<br>Schedule B.<br>Volasertib 200<br>mg |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                                     | Reporting group                                     | Reporting group                                | Reporting group                                |
| Number of subjects analysed                         | 8   | 3   | 10   | 1 <sup>[16]</sup>                              |
| Units: Liter (L)                                    |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 5270 ( $\pm$ 58.2)                                  | 4830 ( $\pm$ 56.7)                                  | 10300 ( $\pm$ 36.3)                            | 9999 ( $\pm$ 9999)                             |

Notes:

[16] - 9999 = Not calculable with one subject

| End point values | Phase I | Phase I | Phase I | Phase I |
|------------------|---------|---------|---------|---------|
|------------------|---------|---------|---------|---------|

|   | Schedule B.<br>Volasertib 350<br>mg | Schedule B.<br>Volasertib 400<br>mg | Schedule B.<br>Volasertib 450<br>mg | Schedule B.<br>Volasertib 500<br>mg |
|---|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type                                  | Reporting group                     | Reporting group                     | Reporting group                     | Reporting group                     |
| Number of subjects analysed                         | 5                                   | 6                                   | 22                                  | 5                                   |
| Units: Liter (L)                                    |                                     |                                     |                                     |                                     |
| geometric mean (geometric coefficient of variation) | 5800 ( $\pm$ 35.1)                  | 7150 ( $\pm$ 70.6)                  | 5740 ( $\pm$ 38.7)                  | 6360 ( $\pm$ 50.1)                  |

| End point values                                    | Phase I<br>Schedule B.<br>Volasertib 550<br>mg | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|---|--|--|--|--|
| Subject group type                                  | Reporting group                                | Reporting group                                      |  |  |
| Number of subjects analysed                         | 3  | 31   |  |  |
| Units: Liter (L)                                    |  |  |  |  |
| geometric mean (geometric coefficient of variation) | 5680 ( $\pm$ 81.9)                             | 6130 ( $\pm$ 42.0)                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Dose normalized maximum measured concentration of cytarabine in plasma (Cmax, norm)

|                 |   |
|-----------------|---|
| End point title | Dose normalized maximum measured concentration of cytarabine in plasma (Cmax, norm) <sup>[17]</sup> |
|-----------------|---|

End point description:

Cmax, norm: Maximum measured concentration of Cytarabine in plasma. The dose normalisation was done by dividing by the dose applied. Unit: nanogram/milliliter/milligram: ((ng/mL)/mg). Dose groups of Phase I were combined by dose normalizing as pre specified in the study protocol. Pharmacokinetic (PK) set which included all patients in the treated set who had at least 1 evaluable blood sample during cycle 1, Only participants with non-missing values are reported.

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

End point timeframe:

Cycle 1: -0:05 hour (h), 0:30h, 1:00h, 1:30h, 2h, 3h, 4h, 24h, 96h, 216h, 335:55h, 336:30h, 337h, 337:30h, 338h, 339h, 340h, 648h after first drug administration.

Notes:

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

Justification: As pre-specified in the protocol this end point Phase IA arms were combined and compared to the Phase II C and Phase II A (350 mg) arms.

| End point values                                    | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Dose norm<br>Volasertib+LDA<br>C (Phase I A).<br>150-400 mg<br>Volasertib |  |
|---|---------------------------------|--|---|--|
| Subject group type                                  | Reporting group                 | Reporting group                                      | Subject analysis set  |  |
| Number of subjects analysed                         | 40                              | 41   | 32  |  |
| Units: (ng/mL)/mg                                   |                                 |  |   |  |
| geometric mean (geometric coefficient of variation) | 2.36 ( $\pm$ 77.6)              | 2.83 ( $\pm$ 52.8)                                   | 2.92 ( $\pm$ 61.3)  |  |

of variation)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Dose Normalized Area Under the Concentration-Time Curve of Cytarabine in Plasma Over the Time Interval from 0 Extrapolated up to 4 hours

|                 |  |
|-----------------|--|
| End point title | Dose Normalized Area Under the Concentration-Time Curve of Cytarabine in Plasma Over the Time Interval from 0 Extrapolated up to 4 hours <sup>[18]</sup> |
|-----------------|--|

End point description:

AUC0-4, norm: Area under the concentration-time curve of Cytarabine in plasma over the time interval from zero extrapolated to 4 hours. The dose normalisation was done by dividing by dose applied. Unit: nanogram\*hour/milliliter/milligram: ((ng\*h/mL)/mg). Dose groups of Phase I were combined by dose normalizing as pre specified in the study protocol.

Pharmacokinetic (PK) set which included all patients in the treated set who had at least 1 evaluable blood sample during cycle 1, Only participants with non-missing values are reported.

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

End point timeframe:

Cycle 1: -0:05 hour (h), 0:30h, 1:00h, 1:30h, 2h, 3h, 4h after first drug administration.

Notes:

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

Justification: As pre-specified in the protocol this end point Phase IA arms were combined and compared to the Phase II C and Phase II A (350 mg) arms.

| End point values                                    | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Dose norm<br>Volasertib+LDA<br>C (Phase I A).<br>150-400 mg<br>Volasertib |  |
|---|---------------------------------|--|---|--|
| Subject group type                                  | Reporting group                 | Reporting group                                      | Subject analysis set  |  |
| Number of subjects analysed                         | 40                              | 41   | 32  |  |
| Units: (ng*h/mL)/mg                                 |                                 |  |   |  |
| geometric mean (geometric coefficient of variation) | 3.94 (± 43.8)                   | 4.00 (± 35.6)  | 3.84 (± 30.6)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute QTcF (QT Interval Corrected for Heart Rate Using Fridericia's Formula) Intervals

|                 |   |
|-----------------|---|
| End point title | Absolute QTcF (QT Interval Corrected for Heart Rate Using Fridericia's Formula) Intervals <sup>[19]</sup> |
|-----------------|---|

End point description:

ECG (electrocardiogram) Measurements: Absolute QTcF (QT Interval (interval from the beginning of the QRS complex to the end of the T wave) Corrected for Heart Rate Using Fridericia's Formula) Intervals.

Treated Set-Phase I part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. Only participants with non-missing values are reported. The 350 mg + LDAC arm of phase I and II were combined into one arm to provide maximum information on QT changes and presented together with the Phase I schedule B 450 mg arm, as pre specified in the study protocol.

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

End point timeframe:

Baseline (Days -14 to -1) and day 1 (1 hour and 24 hours) after start of infusion.

Notes:

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

Justification: As pre-specified in the protocol only arms with sufficient subject numbers were included in this endpoint.

| End point values                     | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I+II<br>Volasertib 350<br>mg+LDAC |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Reporting group                                | Subject analysis set                    |  |  |
| Number of subjects analysed          | 23   | 50                                      |  |  |
| Units: milliseconds (ms)             |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| Individual baseline                  | 412.4 (± 18.7)                                 | 411.6 (± 20.7)                          |  |  |
| 1 hour after start of infusion       | 441.1 (± 20.0)                                 | 430.0 (± 20.4)                          |  |  |
| 24 hour after start of infusion      | 411.9 (± 18.4)                                 | 414.0 (± 21.3)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: QTcF (QT Interval Corrected for Heart Rate Using Fridericia's Formula) Change from Baseline at Cycle 1

|                 |  |
|-----------------|--|
| End point title | QTcF (QT Interval Corrected for Heart Rate Using Fridericia's Formula) Change from Baseline at Cycle 1 <sup>[20]</sup> |
|-----------------|--|

End point description:

ECG Measurements: QTcF (QT Interval (interval from the beginning of the QRS complex to the end of the T wave) changes from baseline at each time point: The QTcF post baseline measurement obtained at time t minus baseline QTcF measurement.

Treated Set-Phase I part: Treated Set was defined as all patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. Only participants with non-missing values are reported. The 350 mg + LDAC arm of phase I and II were combined into one arm to provide maximum information on QT changes and presented together with the Phase I schedule B 450 mg arm, as pre specified in the study protocol.

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

End point timeframe:

Baseline (Days -14 to -1) and day 1 (1 hour and 24 hours) after start of infusion.

Notes:

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

Justification: As pre-specified in the protocol only arms with sufficient subject numbers were included in this endpoint.

| End point values                     | Phase I<br>Schedule B.<br>Volasertib 450<br>mg | Phase I+II<br>Volasertib 350<br>mg+LDAC |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Reporting group                                | Subject analysis set                    |  |  |
| Number of subjects analysed          | 23   | 50                                      |  |  |
| Units: millisecond (ms)              |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| Change from baseline after 1 hour    | 29.6 (± 8.1)                                   | 18.5 (± 10.4)                           |  |  |
| Change from baseline after 24 hour   | -0.5 (± 9.8)                                   | 1.9 (± 10.5)                            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I Schedule A: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade ≥3 during Cycle 1

|                 |   |
|-----------------|---|
| End point title | Phase I Schedule A: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade ≥3 during Cycle 1 <sup>[21]</sup> |
|-----------------|---|

End point description:

Number of patients with AEs following in the categories 3 (severe AE), 4 (life-threatening or disabling AE), 5 (death related AE) of CTCAE is reported.

Treated set-Phase I part: Treated set was defined as all patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason.

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

End point timeframe:

First treatment cycle, up to 28 days.

Notes:

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

Justification: This endpoint only considers the Phase IA arms, other arms are reported in a separate endpoint.

| End point values            | Phase I<br>Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 200<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 300<br>mg+LDAC |
|-----------------------------|---|---|---|---|
| Subject group type          | Reporting group                                     | Reporting group                                     | Reporting group                                     | Reporting group                                     |
| Number of subjects analysed | 4   | 3   | 5   | 9   |
| Units: Participants         |   |   |   |   |
| Grade 3                     | 0   | 0   | 1   | 1   |
| Grade 4                     | 2   | 3   | 3   | 5   |
| Grade 5                     | 0   | 0   | 0   | 3   |

| End point values | Phase I<br>Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I<br>Schedule A.<br>Volasertib+LDA<br>C |  |
|------------------|---|---|---|--|
|------------------|---|---|---|--|

|                             |                 |                 |                      |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 8               | 3               | 32                   |  |
| Units: Participants         |                 |                 |                      |  |
| Grade 3                     | 2               | 1               | 5                    |  |
| Grade 4                     | 3               | 1               | 17                   |  |
| Grade 5                     | 2               | 1               | 6                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I Schedule B: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during Cycle 1

|                 |   |
|-----------------|---|
| End point title | Phase I Schedule B: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during Cycle 1 <sup>[22]</sup> |
|-----------------|---|

End point description:

Number of patients with AEs following in the categories 3 (severe AE), 4 (life-threatening or disabling AE), 5 (death related AE) of CTCAE is reported.

Treated set-Phase I part: Treated set was defined as all patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason.

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

End point timeframe:

First treatment cycle, up to 28 days.

Notes:

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

Justification: This endpoint only considers the Phase IB arms, other arms are reported in a separate endpoint.

| End point values            | Phase I Schedule B. Volasertib 150 mg | Phase I Schedule B. Volasertib 200 mg | Phase I Schedule B. Volasertib 350 mg | Phase I Schedule B. Volasertib 400 mg |
|-----------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Subject group type          | Reporting group                       | Reporting group                       | Reporting group                       | Reporting group                       |
| Number of subjects analysed | 11                                    | 2                                     | 5                                     | 6                                     |
| Units: Participants         |                                       |                                       |                                       |                                       |
| Grade 3                     | 5                                     | 0                                     | 1                                     | 0                                     |
| Grade 4                     | 4                                     | 1                                     | 3                                     | 4                                     |
| Grade 5                     | 1                                     | 1                                     | 0                                     | 0                                     |

| End point values            | Phase I Schedule B. Volasertib 450 mg | Phase I Schedule B. Volasertib 500 mg | Phase I Schedule B. Volasertib 550 mg | Phase I Schedule B. Volasertib |
|-----------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------|
| Subject group type          | Reporting group                       | Reporting group                       | Reporting group                       | Subject analysis set           |
| Number of subjects analysed | 23                                    | 5                                     | 4                                     | 56                             |
| Units: Participants         |                                       |                                       |                                       |                                |

|         |    |   |   |    |
|---------|----|---|---|----|
| Grade 3 | 5  | 0 | 0 | 11 |
| Grade 4 | 14 | 1 | 3 | 30 |
| Grade 5 | 2  | 1 | 1 | 6  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I Schedule A: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during all cycles

|                 |  |
|-----------------|--|
| End point title | Phase I Schedule A: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during all cycles <sup>[23]</sup> |
|-----------------|--|

End point description:

Number of patients with AEs following in the categories 3 (severe AE), 4 (life-threatening or disabling AE), 5 (death related AE) of CTCAE is reported.

Treated set-Phase I part: Treated set was defined as all patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason.

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

End point timeframe:

From first drug administration until 21 days after the last trial drug administration in the last treatment cycle, up to 615 days.

Notes:

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

Justification: This endpoint only considers the Phase IA arms, other arms are reported in a separate endpoint.

| End point values            | Phase I Schedule A. Volasertib 150 mg+LDAC | Phase I Schedule A. Volasertib 200 mg+LDAC | Phase I Schedule A. Volasertib 250 mg+LDAC | Phase I Schedule A. Volasertib 300 mg+LDAC |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group                            | Reporting group                            |
| Number of subjects analysed | 4  | 3  | 5  | 9  |
| Units: Participants         |  |  |  |  |
| Grade 3                     | 1  | 0  | 0  | 1  |
| Grade 4                     | 1  | 3  | 5  | 5  |
| Grade 5                     | 1  | 0  | 0  | 3  |

| End point values            | Phase I Schedule A. Volasertib 350 mg+LDAC | Phase I Schedule A. Volasertib 400 mg+LDAC | Phase I Schedule A. Volasertib+LDA C |  |
|-----------------------------|--|--|--------------------------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Subject analysis set                 |  |
| Number of subjects analysed | 8  | 3  | 32                                   |  |
| Units: Participants         |  |  |                                      |  |
| Grade 3                     | 2  | 1  | 5                                    |  |
| Grade 4                     | 3  | 1  | 18                                   |  |
| Grade 5                     | 2  | 1  | 7                                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase I Schedule B: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during all cycles

|                 |  |
|-----------------|--|
| End point title | Phase I Schedule B: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during all cycles <sup>[24]</sup> |
|-----------------|--|

End point description:

Number of patients with AEs following in the categories 3 (severe AE), 4 (life-threatening or disabling AE), 5 (death related AE) of CTCAE is reported.

Treated set-Phase I part: the treated set was defined as all patients in Phase I who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason.

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

End point timeframe:

From first drug administration until 21 days after the last trial drug administration in the last treatment cycle, up to 597 days.

Notes:

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

Justification: This endpoint only considers the Phase IB arms, other arms are reported in a separate endpoint.

| End point values            | Phase I Schedule B. Volasertib 150 mg | Phase I Schedule B. Volasertib 200 mg | Phase I Schedule B. Volasertib 350 mg | Phase I Schedule B. Volasertib 400 mg |
|-----------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Subject group type          | Reporting group                       | Reporting group                       | Reporting group                       | Reporting group                       |
| Number of subjects analysed | 11                                    | 2                                     | 5                                     | 6                                     |
| Units: Participants         |                                       |                                       |                                       |                                       |
| Grade 3                     | 5                                     | 0                                     | 1                                     | 0                                     |
| Grade 4                     | 4                                     | 1                                     | 3                                     | 5                                     |
| Grade 5                     | 2                                     | 1                                     | 0                                     | 0                                     |

| End point values            | Phase I Schedule B. Volasertib 450 mg | Phase I Schedule B. Volasertib 500 mg | Phase I Schedule B. Volasertib 550 mg | Phase I Schedule B. Volasertib |
|-----------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------|
| Subject group type          | Reporting group                       | Reporting group                       | Reporting group                       | Subject analysis set           |
| Number of subjects analysed | 23                                    | 5                                     | 4                                     | 56                             |
| Units: Participants         |                                       |                                       |                                       |                                |
| Grade 3                     | 3                                     | 0                                     | 0                                     | 9                              |
| Grade 4                     | 15                                    | 1                                     | 3                                     | 32                             |
| Grade 5                     | 3                                     | 2                                     | 1                                     | 9                              |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Phase II: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during all cycles

|                 |  |
|-----------------|--|
| End point title | Phase II: Incidence and Intensity of Adverse Events (AEs) Graded According to Common Terminology Criteria for Adverse Events (CTCAE), based on the number of patients with AEs with CTCAE Grade $\geq 3$ during all cycles <sup>[25]</sup> |
|-----------------|--|

#### End point description:

Number of patients with AEs following in the in the categories 3 (severe AE), 4 (life-threatening or disabling AE), 5 (death related AE) of CTCAE is reported.

Treated set-Phase II part: the treated set (Phase II) was defined as all patients in Phase II who received at least a single dose of either Volasertib or LDAC.

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

#### End point timeframe:

From first drug administration until 21 days after the last trial drug administration in the last treatment cycle, up to 890 days.

#### Notes:

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

Justification: This endpoint only considers the Phase II arms, other arms are reported in a separate endpoint.

| End point values            | Phase II<br>Schedule C.<br>LDAC | Phase II<br>Schedule A.<br>Volasertib 350<br>mg+LDAC |  |  |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type          | Reporting group                 | Reporting group                                      |  |  |
| Number of subjects analysed | 45                              | 42   |  |  |
| Units: Participants         |                                 |  |  |  |
| Grade 3                     | 13                              | 12   |  |  |
| Grade 4                     | 13                              | 20   |  |  |
| Grade 5                     | 6                               | 8  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 21 days after the last trial drug administration in the last treatment cycle, up to 3325 days.

Adverse event reporting additional description:

Treated Set-phase I part: patients who received at least a single dose of either Volasertib or LDAC, including patients who were replaced for any reason. Phase I: all patients who received at least a single dose of either Volasertib or LDAC.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Phase I Schedule A. Volasertib 150 mg+LDAC |
|-----------------------|--|

Reporting group description:

Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Phase II Schedule C. LDAC |
|-----------------------|---------------------------|

Reporting group description:

Low-dose cytarabine (LDAC) monotherapy 2x20 milligram (mg) per day administered by subcutaneous injection on days 1-10 of each 28 days treatment cycle.

|                       |  |
|-----------------------|--|
| Reporting group title | Phase I Schedule A. Volasertib 200 mg+LDAC |
|-----------------------|--|

Reporting group description:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |  |
|-----------------------|--|
| Reporting group title | Phase I Schedule A. Volasertib 250 mg+LDAC |
|-----------------------|--|

Reporting group description:

Volasertib 250 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |  |
|-----------------------|--|
| Reporting group title | Phase I Schedule A. Volasertib 300 mg+LDAC |
|-----------------------|--|

Reporting group description:

Volasertib 300 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |   |
|-----------------------|---|
| Reporting group title | Phase II Schedule A. Volasertib 350 mg+LDAC |
|-----------------------|---|

Reporting group description:

Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |  |
|-----------------------|--|
| Reporting group title | Phase I Schedule A. Volasertib 350 mg+LDAC |
|-----------------------|--|

Reporting group description:

Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |  |
|-----------------------|--|
| Reporting group title | Phase I Schedule A. Volasertib 400 mg+LDAC |
|-----------------------|--|

Reporting group description:

Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle) and Low-dose cytarabine (LDAC) 2x20mg per day administered by subcutaneous injection on days 1-10 of each 28 day treatment cycle.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 400 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 400 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 350 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 350 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 150 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 150 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 200 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 200 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 500 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 500 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 450 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 450 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase I Schedule B. Volasertib 550 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Volasertib 550 milligram (mg) administered by Intravenous Infusion (IV) over 60 minutes on Days 1 and 15 (28-day cycle).

| <b>Serious adverse events</b>                                       | Phase I Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase II Schedule C.<br>LDAC | Phase I Schedule A.<br>Volasertib 200<br>mg+LDAC |
|---|--|------------------------------|--|
| Total subjects affected by serious adverse events                   |  |                              |  |
| subjects affected / exposed   | 2 / 4 (50.00%)                                   | 29 / 45 (64.44%)             | 3 / 3 (100.00%)                                  |
| number of deaths (all causes)                                       | 4  | 45                           | 3  |
| number of deaths resulting from adverse events                      | 0  | 0                            | 0  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                              |  |
| Acute myeloid leukaemia   |  |                              |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                                    | 0 / 45 (0.00%)               | 0 / 3 (0.00%)                                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0                        | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                        | 0 / 0  |
| Malignant neoplasm progression                                      |  |                              |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                                    | 1 / 45 (2.22%)               | 0 / 3 (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  |
| Neoplasm malignant  |  |                              |  |

|  |               |                |               |
|--|---------------|----------------|---------------|
| subjects affected / exposed                          | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Central nervous system leukaemia                     |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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                                   |               |                |               |
| Circulatory collapse                                 |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Deep vein thrombosis                                 |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Haemorrhage  |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Hypotension  |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Surgical and medical procedures                      |               |                |               |
| Catheterisation venous                               |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| General disorders and administration site conditions |               |                |               |
| Asthenia   |               |                |               |
| subjects affected / exposed                          | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| 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 physical health deterioration           |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 5 / 45 (11.11%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 6           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hypothermia                                     |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Mucosal haemorrhage                             |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%)  | 0 / 3 (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          |
| Mucosal inflammation                            |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%)  | 0 / 3 (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          |
| Pain  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pyrexia   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 8 / 45 (17.78%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 8           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Multiple organ dysfunction syndrome             |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Oedema peripheral                               |               |                 |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| 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 |                |                |                |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (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 exertional                             |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperventilation                                |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| 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 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |               |
|---|----------------|----------------|---------------|
| Lung infiltration                               |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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 oedema                                |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Respiratory failure                             |                |                |               |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (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         |
| Psychiatric disorders                           |                |                |               |
| Acute psychosis                                 |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Confusional state                               |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Depression                                      |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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                                  |                |                |               |
| Brain natriuretic peptide increased             |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| C-reactive protein increased<br>subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Oxygen saturation decreased<br>subjects affected / exposed  | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Injury, poisoning and procedural<br>complications           |               |                |               |
| Meniscus injury   |               |                |               |
| subjects affected / exposed                                 | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Subdural haematoma  |               |                |               |
| subjects affected / exposed                                 | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardiac disorders   |               |                |               |
| Acute coronary syndrome                                     |               |                |               |
| subjects affected / exposed                                 | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Acute myocardial infarction                                 |               |                |               |
| subjects affected / exposed                                 | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Angina pectoris   |               |                |               |
| subjects affected / exposed                                 | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |
| Angina unstable   |               |                |               |
| subjects affected / exposed                                 | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0         |



|   |               |                |                |
|---|---------------|----------------|----------------|
| Arrhythmia                                      |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| 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 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| 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 congestive                      |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Long QT syndrome                                |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Myocardial ischaemia                            |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Ventricular fibrillation                        |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |               |                |                |
| Cerebral haemorrhage                            |               |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Dizziness                                       |               |                |                |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Headache  |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (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         |
| Hypoaesthesia                                   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Neuralgia                                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Somnolence                                      |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Syncope   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Seizure   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders            |               |                |               |
| Anaemia   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 3 / 3          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Bone marrow failure                             |               |                |               |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Febrile bone marrow aplasia                     |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Febrile neutropenia                             |                |                 |                |
| subjects affected / exposed                     | 2 / 4 (50.00%) | 6 / 45 (13.33%) | 2 / 3 (66.67%) |
| occurrences causally related to treatment / all | 0 / 3          | 5 / 9           | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Leukocytosis                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| 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 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Neutropenia                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| 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 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (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          |
| Thrombocytopenia                                |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 45 (4.44%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| Ear and labyrinth disorders                     |                |                 |                |
| Vertigo   |                |                 |                |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders                      |               |                |               |
| Abdominal pain                                  |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Anal haemorrhage                                |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Constipation                                    |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Diarrhoea                                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Diarrhoea haemorrhagic                          |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal disorder                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal haemorrhage                    |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Haemorrhoids                                    |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Ileus   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Mouth ulceration                                |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Tongue haematoma                                |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Upper gastrointestinal haemorrhage              |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Vomiting  |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastritis erosive                               |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nausea  |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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                         |               |                |               |
| Hepatic failure                                 |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Skin and subcutaneous tissue disorders          |               |                |               |
| Dermatitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Dermatitis allergic                             |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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                     |               |                |               |
| Dysuria   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nephropathy                                     |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Renal failure                                   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Urinary retention                               |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders |               |                |               |
| Back pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Bone pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Crystal arthropathy                             |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Muscular weakness                               |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal chest pain                      |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Pain in extremity                               |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Polyarthritis                                   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Infections and infestations                     |               |                |               |
| Abscess   |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Abscess neck                                    |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Arthritis bacterial                             |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Aspergillus infection                           |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Bacterial pyelonephritis                        |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Bronchitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Cellulitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 4 / 4          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cerebral fungal infection                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Clostridium difficile infection                 |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cystitis  |               |                |               |



|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Device related infection                        |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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                                    |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Erysipelas                                      |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Escherichia sepsis                              |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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 norovirus                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Infection                                       |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Lung infection                                  |               |                |               |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenic sepsis                              |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 45 (4.44%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 0          |
| Pneumonia fungal                                |                |                |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pseudomembranous colitis                        |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pseudomonal sepsis                              |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| 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 mycosis                               |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory syncytial virus infection           |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis  |                |                |                |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 1 / 4 (25.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0         |
| Soft tissue infection                           |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Staphylococcal infection                        |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Stenotrophomonas infection                      |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Tonsillitis                                     |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Urinary tract infection                         |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (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         |
| Urosepsis                                       |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (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         |
| Klebsiella sepsis                               |                |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Metabolism and nutrition disorders              |                |                |               |
| Dehydration                                     |                |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (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         |
| Hypoalbuminaemia                                |               |                |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| 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>                                       | Phase I Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I Schedule A.<br>Volasertib 300<br>mg+LDAC | Phase II Schedule A.<br>Volasertib 350<br>mg+LDAC |
|---|--|--|---|
| Total subjects affected by serious adverse events                   |  |  |   |
| subjects affected / exposed   | 3 / 5 (60.00%)                                   | 7 / 9 (77.78%)                                   | 34 / 42 (80.95%)                                  |
| number of deaths (all causes)                                       | 4  | 9  | 38  |
| number of deaths resulting from adverse events                      | 0  | 1  | 6   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |   |
| Acute myeloid leukaemia   |  |  |   |
| subjects affected / exposed   | 0 / 5 (0.00%)                                    | 0 / 9 (0.00%)                                    | 0 / 42 (0.00%)                                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0  | 0 / 0   |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0  | 0 / 0   |
| Malignant neoplasm progression                                      |  |  |   |
| subjects affected / exposed   | 0 / 5 (0.00%)                                    | 1 / 9 (11.11%)                                   | 2 / 42 (4.76%)                                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1  | 0 / 2   |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 1  | 0 / 2   |
| Neoplasm malignant  |  |  |   |
| subjects affected / exposed   | 0 / 5 (0.00%)                                    | 0 / 9 (0.00%)                                    | 0 / 42 (0.00%)                                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0  | 0 / 0   |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0  | 0 / 0   |
| Central nervous system leukaemia                                    |  |  |   |
| subjects affected / exposed   | 0 / 5 (0.00%)                                    | 0 / 9 (0.00%)                                    | 1 / 42 (2.38%)                                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0  | 0 / 1   |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0  | 0 / 0   |
| Vascular disorders  |  |  |   |
| Circulatory collapse  |  |  |   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Deep vein thrombosis                                 |                |                |                |
| subjects affected / exposed                          | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (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          |
| Haemorrhage  |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension  |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| 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                      |                |                |                |
| Catheterisation venous                               |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| 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 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General physical health deterioration                |                |                |                |
| subjects affected / exposed                          | 1 / 5 (20.00%) | 2 / 9 (22.22%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          | 0 / 0          |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| Hypothermia                                     |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Mucosal haemorrhage                             |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Mucosal inflammation                            |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pain  |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Pyrexia   |                |               |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 5 / 42 (11.90%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 3 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Multiple organ dysfunction syndrome             |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Oedema peripheral                               |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0           |
| Immune system disorders                         |                |               |                 |
| Hypersensitivity                                |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| 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                                       |               |               |                |
| Dyspnoea  |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| 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 exertional                             |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Epistaxis                                       |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hyperventilation                                |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hypoxia   |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 1          |
| Interstitial lung disease                       |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Lung infiltration                               |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| 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 oedema                                |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Respiratory distress                            |               |               |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 2          |
| Psychiatric disorders                           |                |                |                |
| Acute psychosis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Confusional state                               |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Brain natriuretic peptide increased             |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| C-reactive protein increased                    |                |                |                |
| subjects affected / exposed                     | 3 / 5 (60.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oxygen saturation decreased                     |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| 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                                   |                |                |                |
| Meniscus injury                                 |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Subdural haematoma                              |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| Cardiac disorders                               |                |                |                |
| Acute coronary syndrome                         |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| 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 pectoris                                 |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| 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 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arrhythmia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure                                 |                |                |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 1 / 1          |

|   |               |               |                |
|---|---------------|---------------|----------------|
| Cardiac failure congestive                      |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Long QT syndrome                                |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Myocardial infarction                           |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Myocardial ischaemia                            |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Ventricular fibrillation                        |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Nervous system disorders                        |               |               |                |
| Cerebral haemorrhage                            |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Dizziness                                       |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Headache  |               |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hypoaesthesia                                   |               |               |                |

|   |               |               |                 |
|---|---------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Neuralgia                                       |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Somnolence                                      |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Syncope   |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Seizure   |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Blood and lymphatic system disorders            |               |               |                 |
| Anaemia   |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 5 / 42 (11.90%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 4 / 5           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Bone marrow failure                             |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Febrile bone marrow aplasia                     |               |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0           |
| Febrile neutropenia                             |               |               |                 |

|   |                |                |                  |
|---|----------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 23 / 42 (54.76%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 2          | 22 / 27          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 2 / 2            |
| Leukocytosis                                    |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| 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 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0            |
| Neutropenia                                     |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0            |
| Pancytopenia                                    |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0            |
| Thrombocytopenia                                |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 5 / 42 (11.90%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 5 / 5            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0            |
| Ear and labyrinth disorders                     |                |                |                  |
| Vertigo   |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0            |
| Gastrointestinal disorders                      |                |                |                  |
| Abdominal pain                                  |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0            |
| Anal haemorrhage                                |                |                |                  |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 0 / 42 (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          |
| Constipation                                    |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Diarrhoea                                       |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 2 / 42 (4.76%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Diarrhoea haemorrhagic                          |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Gastrointestinal disorder                       |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Haemorrhoids                                    |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Ileus   |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Mouth ulceration                                |                |               |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Tongue haematoma                                |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Vomiting  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastritis erosive                               |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Nausea  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |               |                |                |
| Hepatic failure                                 |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |               |                |                |
| Dermatitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Dermatitis allergic                             |               |                |                |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Renal and urinary disorders                     |                |               |                |
| Dysuria   |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 0 / 42 (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          |
| Nephropathy                                     |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Renal failure                                   |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Urinary retention                               |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |               |                |
| Back pain                                       |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Bone pain                                       |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Crystal arthropathy                             |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Muscular weakness                               |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Musculoskeletal chest pain                      |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Osteoarthritis                                  |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Pain in extremity                               |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Polyarthritis                                   |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Infections and infestations                     |                |               |                |
| Abscess   |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Abscess neck                                    |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Arthritis bacterial                             |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Aspergillus infection                           |                |               |                |



|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Bacterial pyelonephritis                        |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Bronchitis                                      |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Cellulitis                                      |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Cerebral fungal infection                       |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Clostridium difficile infection                 |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Cystitis  |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Device related infection                        |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Endocarditis                                    |                |               |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Erysipelas                                      |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Escherichia sepsis                              |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastroenteritis norovirus                       |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| 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 / 5 (0.00%) | 1 / 9 (11.11%) | 0 / 42 (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          |
| Infection                                       |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Lung infection                                  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Neutropenic sepsis                              |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia                                       |               |                |                |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 8 / 42 (19.05%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 3 / 11          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 1 / 3           |
| Pneumonia fungal                                |                |                |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pseudomembranous colitis                        |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pseudomonal sepsis                              |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary mycosis                               |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| 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 syncytial virus infection           |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sepsis  |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Soft tissue infection                           |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Staphylococcal infection                        |                |                |                 |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Stenotrophomonas infection                      |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Tonsillitis                                     |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Urinary tract infection                         |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Urosepsis                                       |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Klebsiella sepsis                               |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Metabolism and nutrition disorders              |                |               |                |
| Dehydration                                     |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Hypoalbuminaemia                                |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%) | 1 / 42 (2.38%) |
| 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>Serious adverse events</b> | Phase I Schedule A. | Phase I Schedule A. | Phase I Schedule B. |
|-------------------------------|---------------------|---------------------|---------------------|

|   | Volasertib 350<br>mg+LDAC | Volasertib 400<br>mg+LDAC | Volasertib 400 mg |
|---|---------------------------|---------------------------|-------------------|
| Total subjects affected by serious adverse events                   |                           |                           |                   |
| subjects affected / exposed   | 6 / 8 (75.00%)            | 3 / 3 (100.00%)           | 3 / 6 (50.00%)    |
| number of deaths (all causes)                                       | 8                         | 3                         | 6                 |
| number of deaths resulting from adverse events                      | 0                         | 0                         | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                           |                   |
| Acute myeloid leukaemia   |                           |                           |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)             | 0 / 3 (0.00%)             | 0 / 6 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0             |
| Malignant neoplasm progression                                      |                           |                           |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)             | 0 / 3 (0.00%)             | 0 / 6 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0             |
| Neoplasm malignant  |                           |                           |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)             | 0 / 3 (0.00%)             | 0 / 6 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0             |
| Central nervous system leukaemia                                    |                           |                           |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)             | 0 / 3 (0.00%)             | 0 / 6 (0.00%)     |
| 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  |                           |                           |                   |
| Circulatory collapse  |                           |                           |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)             | 0 / 3 (0.00%)             | 0 / 6 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0             |
| Deep vein thrombosis  |                           |                           |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)             | 0 / 3 (0.00%)             | 0 / 6 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 0                     | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                     | 0 / 0             |
| Haemorrhage   |                           |                           |                   |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Hypotension  |                |                |               |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| 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                      |                |                |               |
| Catheterisation venous                               |                |                |               |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions |                |                |               |
| Asthenia   |                |                |               |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| 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 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| 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 physical health deterioration                |                |                |               |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 1          | 0 / 0         |
| Hypothermia  |                |                |               |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Mucosal haemorrhage                                  |                |                |               |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Mucosal inflammation                            |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain  |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Multiple organ dysfunction syndrome             |                |                |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (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          |
| Oedema peripheral                               |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (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          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| 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 exertional                             |                |                |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (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          |

|   |               |               |               |
|---|---------------|---------------|---------------|
| Epistaxis                                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Hyperventilation                                |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Hypoxia   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Lung infiltration                               |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 oedema                                |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Respiratory failure                             |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Psychiatric disorders                           |               |               |               |



|   |                |               |               |
|---|----------------|---------------|---------------|
| Acute psychosis                                 |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Confusional state                               |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Depression                                      |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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                                  |                |               |               |
| Brain natriuretic peptide increased             |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| C-reactive protein increased                    |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Oxygen saturation decreased                     |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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  |                |               |               |
| Meniscus injury                                 |                |               |               |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Subdural haematoma                              |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Cardiac disorders                               |                |               |                |
| Acute coronary syndrome                         |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Acute myocardial infarction                     |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (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          |
| Angina pectoris                                 |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| 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 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Arrhythmia                                      |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| 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 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| 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 congestive                      |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Long QT syndrome                                |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Myocardial infarction                           |                |               |                |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Myocardial ischaemia                            |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Ventricular fibrillation                        |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Nervous system disorders                        |               |               |               |
| Cerebral haemorrhage                            |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Dizziness                                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Headache  |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Hypoaesthesia                                   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Neuralgia                                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Somnolence                                      |               |               |               |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bone marrow failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile bone marrow aplasia                     |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 3 / 8 (37.50%) | 2 / 3 (66.67%) | 2 / 6 (33.33%) |
| occurrences causally related to treatment / all | 0 / 4          | 1 / 2          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Leukocytosis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| 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 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Neutropenia                                     |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Ear and labyrinth disorders                     |               |               |               |
| Vertigo   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Gastrointestinal disorders                      |               |               |               |
| Abdominal pain                                  |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Anal haemorrhage                                |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Constipation                                    |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Diarrhoea                                       |               |               |               |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Diarrhoea haemorrhagic                          |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Gastrointestinal disorder                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Gastrointestinal haemorrhage                    |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Haemorrhoids                                    |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Ileus   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Mouth ulceration                                |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Tongue haematoma                                |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Upper gastrointestinal haemorrhage              |               |               |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Vomiting  |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastritis erosive                               |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nausea  |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| 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                         |               |                |               |
| Hepatic failure                                 |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Skin and subcutaneous tissue disorders          |               |                |               |
| Dermatitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 1 / 3 (33.33%) | 0 / 6 (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         |
| Dermatitis allergic                             |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| 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                     |               |                |               |
| Dysuria   |               |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |               |               |
|---|---------------|---------------|---------------|
| Nephropathy                                     |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Renal failure                                   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Urinary retention                               |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Musculoskeletal and connective tissue disorders |               |               |               |
| Back pain                                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Bone pain                                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Crystal arthropathy                             |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Muscular weakness                               |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Musculoskeletal chest pain                      |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Pain in extremity                               |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Polyarthritis                                   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Infections and infestations                     |               |               |               |
| Abscess   |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Abscess neck                                    |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Arthritis bacterial                             |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Aspergillus infection                           |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Bacterial pyelonephritis                        |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Bronchitis                                      |               |               |               |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Cellulitis                                      |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Cerebral fungal infection                       |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Clostridium difficile infection                 |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Cystitis  |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Device related infection                        |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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                                    |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Erysipelas                                      |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Escherichia sepsis                              |               |               |               |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| 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 norovirus                       |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| 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 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Infection                                       |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Lung infection                                  |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Neutropenic sepsis                              |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Pneumonia                                       |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Pneumonia fungal                                |                |               |                |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 0 / 3 (0.00%) | 0 / 6 (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          |
| Pseudomembranous colitis                        |                |               |                |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Pseudomonal sepsis                              |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 mycosis                               |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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 syncytial virus infection           |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Sepsis  |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Soft tissue infection                           |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Staphylococcal infection                        |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Stenotrophomonas infection                      |               |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Tonsillitis                                     |               |               |               |

|   |                |               |               |
|---|----------------|---------------|---------------|
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Urinary tract infection                         |                |               |               |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Urosepsis                                       |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Klebsiella sepsis                               |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Metabolism and nutrition disorders              |                |               |               |
| Dehydration                                     |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |
| Hypoalbuminaemia                                |                |               |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| 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>                                       | Phase I Schedule B.<br>Volasertib 350 mg | Phase I Schedule B.<br>Volasertib 150 mg | Phase I Schedule B.<br>Volasertib 200 mg |
|---|--|--|--|
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 3 / 5 (60.00%)                           | 7 / 11 (63.64%)                          | 1 / 2 (50.00%)                           |
| number of deaths (all causes)                                       | 3  | 11                                       | 2  |
| number of deaths resulting from adverse events                      | 0  | 1  | 0  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Acute myeloid leukaemia   |  |  |  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Malignant neoplasm progression                  |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 1 / 2 (50.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| Neoplasm malignant                              |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Central nervous system leukaemia                |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| 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                              |                |                |                |
| Circulatory collapse                            |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (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          |
| Deep vein thrombosis                            |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhage                                     |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension                                     |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| 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                 |                |                |                |

|  |               |                |               |
|--|---------------|----------------|---------------|
| Catheterisation venous                               |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions |               |                |               |
| Asthenia   |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 physical health deterioration                |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (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         |
| Hypothermia  |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Mucosal haemorrhage                                  |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Mucosal inflammation                                 |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (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         |
| Pain   |               |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Pyrexia   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (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         |
| Multiple organ dysfunction syndrome             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Oedema peripheral                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Immune system disorders                         |               |                |               |
| Hypersensitivity                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 |               |                |               |
| Dyspnoea  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 exertional                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Epistaxis                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hyperventilation                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |



|   |               |                |               |
|---|---------------|----------------|---------------|
| Hypoxia   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Lung infiltration                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 oedema                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Respiratory failure                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Psychiatric disorders                           |               |                |               |
| Acute psychosis                                 |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Confusional state                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Depression                                      |               |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>                                 |                |                |               |
| Brain natriuretic peptide increased                   |                |                |               |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0         |
| C-reactive protein increased                          |                |                |               |
| subjects affected / exposed                           | 1 / 5 (20.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0         |
| Oxygen saturation decreased                           |                |                |               |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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> |                |                |               |
| Meniscus injury                                       |                |                |               |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0         |
| Subdural haematoma                                    |                |                |               |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 coronary syndrome                               |                |                |               |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0         |
| Acute myocardial infarction                           |                |                |               |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Arrhythmia                                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (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         |
| Cardiac failure congestive                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Long QT syndrome                                |                |                |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (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         |
| Myocardial infarction                           |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Myocardial ischaemia                            |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Ventricular fibrillation                        |                |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nervous system disorders                        |               |                |               |
| Cerebral haemorrhage                            |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Dizziness                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Headache  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hypoaesthesia                                   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Neuralgia                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Somnolence                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Syncope   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Seizure   |               |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>Blood and lymphatic system disorders</b>     |                |                |               |
| <b>Anaemia</b>                                  |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>Bone marrow failure</b>                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>Febrile bone marrow aplasia</b>              |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>Febrile neutropenia</b>                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>Leukocytosis</b>                             |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>Neutropenia</b>                              |                |                |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (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>Pancytopenia</b>                             |                |                |               |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| 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 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Ear and labyrinth disorders                     |               |                |                |
| Vertigo   |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |               |                |                |
| Abdominal pain                                  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Anal haemorrhage                                |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Constipation                                    |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 1 / 2 (50.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Diarrhoea haemorrhagic                          |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastrointestinal disorder                       |               |                |                |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal haemorrhage                    |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Haemorrhoids                                    |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Ileus   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Mouth ulceration                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Tongue haematoma                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Upper gastrointestinal haemorrhage              |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Vomiting  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastritis erosive                               |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nausea  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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                         |               |                |               |
| Hepatic failure                                 |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (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          |               |                |               |
| Dermatitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Dermatitis allergic                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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                     |               |                |               |
| Dysuria   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nephropathy                                     |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Renal failure                                   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |



|   |               |                |               |
|---|---------------|----------------|---------------|
| Urinary retention                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders |               |                |               |
| Back pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Bone pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Crystal arthropathy                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Muscular weakness                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal chest pain                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pain in extremity                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Polyarthritis                                   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Infections and infestations                     |               |                |               |
| Abscess   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Abscess neck                                    |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Arthritis bacterial                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Aspergillus infection                           |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Bacterial pyelonephritis                        |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Bronchitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cellulitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cerebral fungal infection                       |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Clostridium difficile infection                 |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cystitis  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Device related infection                        |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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                                    |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Erysipelas                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Escherichia sepsis                              |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 norovirus                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0         |
| Infection                                       |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0         |
| Lung infection                                  |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0         |
| Neutropenic sepsis                              |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0         |
| Pneumonia                                       |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 3 / 11 (27.27%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0         |
| Pneumonia fungal                                |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 1 / 1           | 0 / 0         |
| Pseudomembranous colitis                        |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0         |
| Pseudomonal sepsis                              |               |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| 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 mycosis                               |               |                 |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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 syncytial virus infection           |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Sepsis  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (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         |
| Soft tissue infection                           |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Staphylococcal infection                        |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Stenotrophomonas infection                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Tonsillitis                                     |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Urinary tract infection                         |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Urosepsis                                       |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Klebsiella sepsis                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Metabolism and nutrition disorders              |               |                |               |
| Dehydration                                     |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hypoalbuminaemia                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| 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>                                       | Phase I Schedule B.<br>Volasertib 500 mg | Phase I Schedule B.<br>Volasertib 450 mg | Phase I Schedule B.<br>Volasertib 550 mg |
|---|--|--|--|
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 3 / 5 (60.00%)                           | 16 / 23 (69.57%)                         | 3 / 4 (75.00%)                           |
| number of deaths (all causes)                                       | 5  | 21                                       | 4  |
| number of deaths resulting from adverse events                      | 1  | 0  | 1  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Acute myeloid leukaemia   |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences causally related to treatment / all                     | 0 / 0                                    | 0 / 0                                    | 0 / 0                                    |
| deaths causally related to treatment / all                          | 0 / 0                                    | 0 / 0                                    | 0 / 0                                    |
| Malignant neoplasm progression                                      |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences causally related to treatment / all                     | 0 / 0                                    | 0 / 0                                    | 0 / 0                                    |
| deaths causally related to treatment / all                          | 0 / 0                                    | 0 / 0                                    | 0 / 0                                    |
| Neoplasm malignant  |  |  |  |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed                          | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (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         |
| Central nervous system leukaemia                     |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (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         |
| Vascular disorders                                   |                |                |               |
| Circulatory collapse                                 |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Deep vein thrombosis                                 |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Haemorrhage  |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Hypotension  |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| 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                      |                |                |               |
| Catheterisation venous                               |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions |                |                |               |
| Asthenia   |                |                |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (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         |

|   |               |                |                |
|---|---------------|----------------|----------------|
| Chest pain                                      |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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 physical health deterioration           |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (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          |
| Hypothermia                                     |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Mucosal haemorrhage                             |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Mucosal inflammation                            |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 2 / 4 (50.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pain  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pyrexia   |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Multiple organ dysfunction syndrome             |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Oedema peripheral                               |               |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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 |                |                |                |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea exertional                             |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (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          |
| Hyperventilation                                |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |               |                |                |
|---|---------------|----------------|----------------|
| Lung infiltration                               |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 1 / 1          |
| Pulmonary oedema                                |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Respiratory failure                             |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |               |                |                |
| Acute psychosis                                 |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Confusional state                               |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Depression                                      |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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                                  |               |                |                |
| Brain natriuretic peptide increased             |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

|   |               |                |                |
|---|---------------|----------------|----------------|
| C-reactive protein increased<br>subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Oxygen saturation decreased<br>subjects affected / exposed  | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural<br>complications           |               |                |                |
| Meniscus injury   |               |                |                |
| subjects affected / exposed                                 | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Subdural haematoma  |               |                |                |
| subjects affected / exposed                                 | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Cardiac disorders   |               |                |                |
| Acute coronary syndrome                                     |               |                |                |
| subjects affected / exposed                                 | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                                 |               |                |                |
| subjects affected / exposed                                 | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Angina pectoris   |               |                |                |
| subjects affected / exposed                                 | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |
| Angina unstable   |               |                |                |
| subjects affected / exposed                                 | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to<br>treatment / all          | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all               | 0 / 0         | 0 / 0          | 0 / 0          |

|   |                |                |               |
|---|----------------|----------------|---------------|
| Arrhythmia                                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| 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 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| 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 congestive                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Long QT syndrome                                |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Myocardial infarction                           |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Myocardial ischaemia                            |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Ventricular fibrillation                        |                |                |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (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         |
| Nervous system disorders                        |                |                |               |
| Cerebral haemorrhage                            |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (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         |
| Dizziness                                       |                |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Headache  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hypoaesthesia                                   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Neuralgia                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Somnolence                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Syncope   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Seizure   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders            |               |                |               |
| Anaemia   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Bone marrow failure                             |               |                |               |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (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          |
| Febrile bone marrow aplasia                     |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Febrile neutropenia                             |                |                 |                |
| subjects affected / exposed                     | 2 / 5 (40.00%) | 9 / 23 (39.13%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 15          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Leukocytosis                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| 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 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Neutropenia                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| 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 / 5 (0.00%)  | 0 / 23 (0.00%)  | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Thrombocytopenia                                |                |                 |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (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          |
| Ear and labyrinth disorders                     |                |                 |                |
| Vertigo   |                |                 |                |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders                      |               |                |               |
| Abdominal pain                                  |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Anal haemorrhage                                |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Constipation                                    |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Diarrhoea                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Diarrhoea haemorrhagic                          |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal disorder                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal haemorrhage                    |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (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         |
| Haemorrhoids                                    |               |                |               |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Ileus   |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (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          |
| Mouth ulceration                                |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Tongue haematoma                                |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Vomiting  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastritis erosive                               |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Nausea  |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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                         |               |                |                |
| Hepatic failure                                 |               |                |                |



|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Skin and subcutaneous tissue disorders          |               |                |               |
| Dermatitis                                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Dermatitis allergic                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| 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                     |               |                |               |
| Dysuria   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nephropathy                                     |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Renal failure                                   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Urinary retention                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders |               |                |               |
| Back pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Bone pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Crystal arthropathy                             |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Muscular weakness                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal chest pain                      |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| 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 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pain in extremity                               |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Polyarthritis                                   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Infections and infestations                     |               |                |               |
| Abscess   |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Abscess neck                                    |               |                |               |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Arthritis bacterial                             |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Aspergillus infection                           |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Bacterial pyelonephritis                        |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Bronchitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cellulitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cerebral fungal infection                       |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Clostridium difficile infection                 |               |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cystitis  |               |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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                                    |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Erysipelas                                      |                |                |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Escherichia sepsis                              |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| 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 norovirus                       |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (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          |
| Herpes zoster                                   |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infection                                       |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lung infection                                  |                |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Neutropenic sepsis                              |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pneumonia                                       |                |                 |                |
| subjects affected / exposed                     | 2 / 5 (40.00%) | 4 / 23 (17.39%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 4           | 1 / 1          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 2           | 1 / 1          |
| Pneumonia fungal                                |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pseudomembranous colitis                        |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pseudomonal sepsis                              |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| 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 mycosis                               |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (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          |
| Respiratory syncytial virus infection           |                |                 |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Sepsis  |                |                 |                |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (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         |
| Soft tissue infection                           |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Staphylococcal infection                        |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Stenotrophomonas infection                      |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Tonsillitis                                     |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Urinary tract infection                         |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Urosepsis                                       |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Klebsiella sepsis                               |                |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Metabolism and nutrition disorders              |                |                |               |
| Dehydration                                     |                |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 23 (4.35%) | 0 / 4 (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>Hypoalbuminaemia</b>                         |               |                |               |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

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

| <b>Non-serious adverse events</b>  | Phase I Schedule A.<br>Volasertib 150<br>mg+LDAC | Phase II Schedule C.<br>LDAC | Phase I Schedule A.<br>Volasertib 200<br>mg+LDAC |
|--|--|------------------------------|--|
| <b>Total subjects affected by non-serious adverse events</b>               |  |                              |  |
| subjects affected / exposed  | 4 / 4 (100.00%)                                  | 43 / 45 (95.56%)             | 3 / 3 (100.00%)                                  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |  |                              |  |
| <b>Chloroma</b>  |  |                              |  |
| subjects affected / exposed  | 0 / 4 (0.00%)                                    | 1 / 45 (2.22%)               | 0 / 3 (0.00%)                                    |
| occurrences (all)  | 0  | 1                            | 0  |
| <b>Leukaemia cutis</b>   |  |                              |  |
| subjects affected / exposed  | 0 / 4 (0.00%)                                    | 0 / 45 (0.00%)               | 0 / 3 (0.00%)                                    |
| occurrences (all)  | 0  | 0                            | 0  |
| <b>Meningioma</b>  |  |                              |  |
| subjects affected / exposed  | 0 / 4 (0.00%)                                    | 0 / 45 (0.00%)               | 0 / 3 (0.00%)                                    |
| occurrences (all)  | 0  | 0                            | 0  |
| <b>Neoplasm progression</b>  |  |                              |  |
| subjects affected / exposed  | 0 / 4 (0.00%)                                    | 0 / 45 (0.00%)               | 0 / 3 (0.00%)                                    |
| occurrences (all)  | 0  | 0                            | 0  |
| <b>Small intestine carcinoma</b>   |  |                              |  |
| subjects affected / exposed  | 0 / 4 (0.00%)                                    | 0 / 45 (0.00%)               | 0 / 3 (0.00%)                                    |
| occurrences (all)  | 0  | 0                            | 0  |
| <b>Vascular disorders</b>  |  |                              |  |
| <b>Angiopathy</b>  |  |                              |  |
| subjects affected / exposed  | 1 / 4 (25.00%)                                   | 0 / 45 (0.00%)               | 0 / 3 (0.00%)                                    |
| occurrences (all)  | 1  | 0                            | 0  |
| <b>Circulatory collapse</b>  |  |                              |  |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Haematoma                   |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Haemorrhage                 |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Hypertension                |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 4 / 45 (8.89%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 4              | 0              |
| Hypertensive crisis         |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Hypotension                 |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 45 (4.44%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 2              | 1              |
| Infarction                  |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Peripheral coldness         |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Peripheral embolism         |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Thrombophlebitis            |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 4 / 45 (8.89%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 4              | 0              |
| Varicose vein               |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Lymphoedema                 |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Phlebitis                   |                |                |                |



|   |                    |                     |                    |
|---|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)        | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |
| Surgical and medical procedures                         |                    |                     |                    |
| Central venous catheterisation                          |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 0                   | 0                  |
| Nail operation  |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 0                   | 0                  |
| General disorders and administration<br>site conditions |                    |                     |                    |
| Adverse drug reaction                                   |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 0                   | 0                  |
| Asthenia  |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 11 / 45 (24.44%)    | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 16                  | 0                  |
| Calcinosis  |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 0                   | 0                  |
| Catheter site erythema                                  |                    |                     |                    |
| subjects affected / exposed                             | 1 / 4 (25.00%)     | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 1                  | 0                   | 0                  |
| Catheter site oedema                                    |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 0                   | 0                  |
| Chest discomfort  |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 0                  | 0                   | 0                  |
| Chest pain  |                    |                     |                    |
| subjects affected / exposed                             | 0 / 4 (0.00%)      | 3 / 45 (6.67%)      | 1 / 3 (33.33%)     |
| occurrences (all)                                       | 0                  | 4                   | 3                  |
| Chills  |                    |                     |                    |
| subjects affected / exposed                             | 1 / 4 (25.00%)     | 1 / 45 (2.22%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                       | 1                  | 1                   | 0                  |
| Fatigue   |                    |                     |                    |

|                                       |                |                  |                |
|---------------------------------------|----------------|------------------|----------------|
| subjects affected / exposed           | 1 / 4 (25.00%) | 11 / 45 (24.44%) | 1 / 3 (33.33%) |
| occurrences (all)                     | 1              | 14               | 1              |
| Feeling cold                          |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Feeling hot                           |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Feeling of body temperature change    |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Gait disturbance                      |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| General physical health deterioration |                |                  |                |
| subjects affected / exposed           | 1 / 4 (25.00%) | 0 / 45 (0.00%)   | 1 / 3 (33.33%) |
| occurrences (all)                     | 1              | 0                | 1              |
| Granuloma                             |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Induration                            |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Inflammation                          |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Influenza like illness                |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 1                | 0              |
| Infusion site pain                    |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Injection site haematoma              |                |                  |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Injection site reaction               |                |                  |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1               | 1              |
| Local swelling              |                |                 |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Localised oedema            |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Malaise                     |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mucosal inflammation        |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 45 (4.44%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Oedema                      |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 2               | 1              |
| Oedema mucosal              |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oedema peripheral           |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 9 / 45 (20.00%) | 2 / 3 (66.67%) |
| occurrences (all)           | 0              | 11              | 3              |
| Pain                        |                |                 |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 3 / 45 (6.67%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 3               | 0              |
| Puncture site pain          |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pyrexia                     |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 8 / 45 (17.78%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 11              | 1              |
| Thirst decreased            |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Peripheral swelling         |                |                 |                |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Catheter site pain                       |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0             |
| Hyperthermia                             |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Discomfort                               |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Mucosal haemorrhage                      |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0             |
| Social circumstances                     |                |                |               |
| Fasting                                  |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Reproductive system and breast disorders |                |                |               |
| Breast enlargement                       |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Genital swelling                         |                |                |               |
| subjects affected / exposed              | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0             |
| Haematospermia                           |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Nipple disorder                          |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Pelvic pain                              |                |                |               |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Penile oedema                            |                |                |               |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Scrotal oedema                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Vaginal haemorrhage                             |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Vulvovaginal erythema                           |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Genital burning sensation                       |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                 |                |
| Atelectasis                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Bronchial secretion retention                   |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Dysphonia                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 1 / 3 (33.33%) |
| occurrences (all)                               | 0              | 1               | 1              |
| Cough   |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 6 / 45 (13.33%) | 1 / 3 (33.33%) |
| occurrences (all)                               | 0              | 8               | 1              |
| Dyspnoea  |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 8 / 45 (17.78%) | 1 / 3 (33.33%) |
| occurrences (all)                               | 0              | 10              | 1              |
| Dyspnoea exertional                             |                |                 |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 1              | 1               | 0              |
| Haemoptysis                                     |                |                 |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 1               | 0              |
| Epistaxis                   |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 9 / 45 (20.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 11              | 0              |
| Hiccups                     |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Laryngeal disorder          |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Lung infiltration           |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Lung disorder               |                |                 |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Nasal inflammation          |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1               | 1              |
| Oropharyngeal pain          |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 45 (4.44%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Pharyngeal inflammation     |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Pleural effusion            |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1               | 1              |
| Productive cough            |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pulmonary hypertension      |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Respiratory failure         |                |                 |                |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Sputum discoloured          |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Sputum retention            |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Vocal cord disorder         |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rales                       |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rhonchi                     |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Throat irritation           |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Psychiatric disorders       |               |                |               |
| Agitation                   |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Anxiety                     |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 2              | 0             |
| Communication disorder      |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Confusional state           |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 2              | 0             |
| Depressed mood              |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 1              | 1              | 0              |
| Disorientation                                  |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Hallucination                                   |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Hallucination, visual                           |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Initial insomnia                                |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Insomnia  |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 4 / 45 (8.89%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 4              | 0              |
| Panic attack                                    |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Restlessness                                    |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Sleep disorder                                  |                |                |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 1 / 45 (2.22%) | 1 / 3 (33.33%) |
| occurrences (all)                               | 1              | 3              | 1              |
| Suicidal ideation                               |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Investigations                                  |                |                |                |
| Activated partial thromboplastin time prolonged |                |                |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Activated partial thromboplastin time shortened |                |                |                |



|  |               |                |                 |
|--|---------------|----------------|-----------------|
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                      | 0             | 0              | 0               |
| Alanine aminotransferase increased     |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 3 / 3 (100.00%) |
| occurrences (all)                      | 0             | 2              | 4               |
| Aspartate aminotransferase increased   |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 2 / 3 (66.67%)  |
| occurrences (all)                      | 0             | 3              | 2               |
| Blast cell count increased             |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                      | 0             | 0              | 0               |
| Blood albumin decreased                |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                      | 0             | 0              | 0               |
| Blood albumin increased                |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                      | 0             | 0              | 0               |
| Blood alkaline phosphatase increased   |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%)  |
| occurrences (all)                      | 0             | 0              | 1               |
| Blood bilirubin increased              |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 2 / 3 (66.67%)  |
| occurrences (all)                      | 0             | 0              | 2               |
| Blood chloride increased               |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                      | 0             | 0              | 0               |
| Blood creatine phosphokinase decreased |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                      | 0             | 0              | 0               |
| Blood creatine phosphokinase increased |               |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%)  |
| occurrences (all)                      | 0             | 0              | 1               |
| Blood creatinine                       |               |                |                 |

|                                       |                |                |                |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood creatinine decreased            |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood creatinine increased            |                |                |                |
| subjects affected / exposed           | 1 / 4 (25.00%) | 3 / 45 (6.67%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 1              | 3              | 0              |
| Blood fibrinogen increased            |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood glucose increased               |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood iron decreased                  |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood iron increased                  |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood lactate dehydrogenase decreased |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood lactate dehydrogenase increased |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                     | 0              | 0              | 1              |
| Blood phosphorus decreased            |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood potassium decreased             |                |                |                |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                     | 0              | 2              | 0              |
| Blood pressure increased              |                |                |                |

|                                |                |                 |                |
|--------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood triglycerides increased  |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood urea decreased           |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood urea increased           |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 3               | 0              |
| Blood uric acid increased      |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 1               | 0              |
| Blood urine present            |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Body temperature increased     |                |                 |                |
| subjects affected / exposed    | 1 / 4 (25.00%) | 2 / 45 (4.44%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 1              | 2               | 0              |
| Breath sounds abnormal         |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| C-reactive protein increased   |                |                 |                |
| subjects affected / exposed    | 2 / 4 (50.00%) | 5 / 45 (11.11%) | 1 / 3 (33.33%) |
| occurrences (all)              | 2              | 6               | 1              |
| Candida test positive          |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Ejection fraction decreased    |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Electrocardiogram QT prolonged |                |                 |                |
| subjects affected / exposed    | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)              | 0              | 0               | 2              |
| Electrocardiogram change       |                |                 |                |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Enterococcus test positive           |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Escherichia test positive            |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Gamma-glutamyltransferase increased  |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all)                    | 0              | 0              | 2              |
| Heart rate increased                 |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Hepatic enzyme increased             |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Liver function test abnormal         |                |                |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0              |
| Oxygen saturation decreased          |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Prostatic specific antigen increased |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Protein total decreased              |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Prothrombin time prolonged           |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Serum ferritin increased             |                |                |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Thrombin time shortened<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Troponin increased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 4 (25.00%)<br>1 | 1 / 45 (2.22%)<br>1 | 1 / 3 (33.33%)<br>1 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 4 (25.00%)<br>1 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| International normalised ratio increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 1 / 45 (2.22%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Allergic transfusion reaction<br>subjects affected / exposed<br>occurrences (all)            | 0 / 4 (0.00%)<br>0  | 1 / 45 (2.22%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Drug administration error<br>subjects affected / exposed<br>occurrences (all)                | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 1 / 3 (33.33%)<br>1 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 4 (0.00%)<br>0  | 1 / 45 (2.22%)<br>2 | 0 / 3 (0.00%)<br>0  |
| Laceration   |                     |                     |                     |

|                                  |               |                |               |
|----------------------------------|---------------|----------------|---------------|
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Lip injury                       |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Procedural pain                  |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 1              | 0             |
| Transfusion reaction             |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 2              | 0             |
| Wound                            |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Skin abrasion                    |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Stoma site haemorrhage           |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Cardiac disorders                |               |                |               |
| Angina pectoris                  |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Aortic valve incompetence        |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Arteriosclerosis coronary artery |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Atrioventricular block           |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Bradycardia                      |               |                |               |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Bundle branch block right   |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiac arrest              |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiac disorder            |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiac failure             |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 2              | 0             |
| Cardiac valve disease       |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiomegaly                |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiomyopathy              |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiovascular disorder     |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Congestive cardiomyopathy   |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Extrasystoles               |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Heart valve incompetence    |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Hypertensive heart disease  |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|   |                    |                     |                     |
|---|--------------------|---------------------|---------------------|
| Left ventricular hypertrophy<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 4 (0.00%)<br>0 | 4 / 45 (8.89%)<br>4 | 0 / 3 (0.00%)<br>0  |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 4 (0.00%)<br>0 | 1 / 45 (2.22%)<br>1 | 1 / 3 (33.33%)<br>1 |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 4 (0.00%)<br>0 | 1 / 45 (2.22%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Nervous system disorders<br>Burning sensation<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Dizziness   |                    |                     |                     |



|                               |                |                 |                |
|-------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed   | 1 / 4 (25.00%) | 2 / 45 (4.44%)  | 1 / 3 (33.33%) |
| occurrences (all)             | 1              | 2               | 1              |
| Headache                      |                |                 |                |
| subjects affected / exposed   | 1 / 4 (25.00%) | 7 / 45 (15.56%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 2              | 9               | 0              |
| Hemiparesis                   |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Orthostatic intolerance       |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Paraesthesia                  |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 3 / 45 (6.67%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 3               | 0              |
| Peripheral sensory neuropathy |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 2 / 45 (4.44%)  | 1 / 3 (33.33%) |
| occurrences (all)             | 0              | 2               | 1              |
| Polyneuropathy                |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)             | 0              | 0               | 1              |
| Sinus headache                |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Somnolence                    |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Syncope                       |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0              |
| Tremor                        |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0              |
| Ageusia                       |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Dysgeusia                     |                |                 |                |

|                                      |                |                  |                |
|--------------------------------------|----------------|------------------|----------------|
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0                | 0              |
| Hypotonia                            |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1                | 0              |
| Blood and lymphatic system disorders |                |                  |                |
| Anaemia                              |                |                  |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 12 / 45 (26.67%) | 2 / 3 (66.67%) |
| occurrences (all)                    | 1              | 31               | 3              |
| Febrile neutropenia                  |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 4 / 45 (8.89%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 6                | 0              |
| Leukocytosis                         |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 3 / 45 (6.67%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 6                | 0              |
| Leukopenia                           |                |                  |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 3 / 45 (6.67%)   | 1 / 3 (33.33%) |
| occurrences (all)                    | 1              | 7                | 2              |
| Lymphadenopathy                      |                |                  |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1              | 0                | 0              |
| Neutropenia                          |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 5 / 45 (11.11%)  | 2 / 3 (66.67%) |
| occurrences (all)                    | 0              | 10               | 2              |
| Splenomegaly                         |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0                | 0              |
| Thrombocytopenia                     |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 8 / 45 (17.78%)  | 2 / 3 (66.67%) |
| occurrences (all)                    | 0              | 26               | 2              |
| Cytopenia                            |                |                  |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 0                | 0              |
| Ear and labyrinth disorders          |                |                  |                |
| Ear haemorrhage                      |                |                  |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Vertigo                     |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Eye disorders               |                |                |                |
| Cataract                    |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Dry eye                     |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 1              | 0              | 1              |
| Erythema of eyelid          |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Eye haemorrhage             |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Eyelid oedema               |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Glaucoma                    |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Lacrimation increased       |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Macular degeneration        |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Visual acuity reduced       |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Visual impairment           |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |

|                             |                |                  |                 |
|-----------------------------|----------------|------------------|-----------------|
| Hyphaema                    |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0              | 0                | 0               |
| Photopsia                   |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0              | 1                | 0               |
| Gastrointestinal disorders  |                |                  |                 |
| Abdominal pain              |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 4 / 45 (8.89%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0              | 6                | 0               |
| Abdominal pain upper        |                |                  |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 4 / 45 (8.89%)   | 1 / 3 (33.33%)  |
| occurrences (all)           | 1              | 4                | 1               |
| Abnormal faeces             |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0              | 0                | 0               |
| Anal haemorrhage            |                |                  |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 1              | 0                | 0               |
| Ascites                     |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0              | 0                | 0               |
| Constipation                |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 12 / 45 (26.67%) | 3 / 3 (100.00%) |
| occurrences (all)           | 0              | 14               | 4               |
| Diarrhoea                   |                |                  |                 |
| subjects affected / exposed | 2 / 4 (50.00%) | 11 / 45 (24.44%) | 2 / 3 (66.67%)  |
| occurrences (all)           | 2              | 14               | 4               |
| Dry mouth                   |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 2 / 3 (66.67%)  |
| occurrences (all)           | 0              | 0                | 2               |
| Dyspepsia                   |                |                  |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 1 / 3 (33.33%)  |
| occurrences (all)           | 0              | 1                | 1               |
| Dysphagia                   |                |                  |                 |

|                               |               |                |                |
|-------------------------------|---------------|----------------|----------------|
| subjects affected / exposed   | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 2 / 3 (66.67%) |
| occurrences (all)             | 0             | 2              | 2              |
| Enterocolitis                 |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Faecaloma                     |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Flatulence                    |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Gastritis                     |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 1              | 0              |
| Gastrointestinal inflammation |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Gingival bleeding             |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 2              | 0              |
| Gingival discolouration       |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Gingival pain                 |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 1              | 0              |
| Gingival swelling             |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Glossodynia                   |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 0              | 0              |
| Haematochezia                 |               |                |                |
| subjects affected / exposed   | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)             | 0             | 1              | 0              |
| Haemorrhoids                  |               |                |                |

|                             |                |                  |                |
|-----------------------------|----------------|------------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Hiatus hernia               |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Mouth haemorrhage           |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 3 / 45 (6.67%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 3                | 0              |
| Mouth ulceration            |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1                | 0              |
| Nausea                      |                |                  |                |
| subjects affected / exposed | 2 / 4 (50.00%) | 16 / 45 (35.56%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 2              | 22               | 0              |
| Oesophagitis                |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Oral mucosal erythema       |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Oral pain                   |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Periodontal disease         |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Proctalgia                  |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1                | 1              |
| Rectal haemorrhage          |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Small intestine ulcer       |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Stomatitis                  |                |                  |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 1               | 0              |
| Tongue coated               |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tongue ulceration           |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Toothache                   |                |                 |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 45 (4.44%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 2               | 0              |
| Vomiting                    |                |                 |                |
| subjects affected / exposed | 2 / 4 (50.00%) | 6 / 45 (13.33%) | 1 / 3 (33.33%) |
| occurrences (all)           | 2              | 7               | 1              |
| Anal incontinence           |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Aphthous ulcer              |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Tongue discolouration       |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Abdominal discomfort        |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gastric ulcer               |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gastrointestinal disorder   |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Palatal disorder            |                |                 |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tongue haemorrhage          |                |                 |                |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |
| Hepatobiliary disorders                          |                    |                     |                    |
| Cholelithiasis                                   |                    |                     |                    |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Hepatic congestion                               |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic cyst                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic lesion                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatomegaly                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hyperbilirubinaemia                              |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 1 / 3 (33.33%)     |
| occurrences (all)                                | 0                  | 0                   | 2                  |
| Hepatic steatosis                                |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Skin and subcutaneous tissue disorders           |                    |                     |                    |
| Alopecia   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Blister  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Blood blister                                    |                    |                     |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 45 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Dermatitis atopic                                |                    |                     |                    |



|                                 |               |                 |                |
|---------------------------------|---------------|-----------------|----------------|
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)               | 0             | 0               | 1              |
| <b>Dermatitis exfoliative</b>   |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 0               | 0              |
| <b>Dry skin</b>                 |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 3 / 45 (6.67%)  | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 3               | 0              |
| <b>Erythema</b>                 |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)               | 0             | 0               | 1              |
| <b>Haemorrhage subcutaneous</b> |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 0               | 0              |
| <b>Hyperhidrosis</b>            |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 2 / 45 (4.44%)  | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 2               | 0              |
| <b>Night sweats</b>             |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 3 / 45 (6.67%)  | 1 / 3 (33.33%) |
| occurrences (all)               | 0             | 3               | 1              |
| <b>Pain of skin</b>             |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 0               | 0              |
| <b>Parapsoriasis</b>            |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 0               | 0              |
| <b>Petechiae</b>                |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 5 / 45 (11.11%) | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 8               | 0              |
| <b>Pruritus</b>                 |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 7 / 45 (15.56%) | 0 / 3 (0.00%)  |
| occurrences (all)               | 0             | 8               | 0              |
| <b>Psoriasis</b>                |               |                 |                |
| subjects affected / exposed     | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)               | 0             | 0               | 1              |
| <b>Purpura</b>                  |               |                 |                |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Rash                        |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 4 / 45 (8.89%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 4              | 0             |
| Skin erosion                |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Skin haemorrhage            |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Skin hyperpigmentation      |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Skin lesion                 |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Swelling face               |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Urticaria                   |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Eczema                      |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Ingrowing nail              |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Intertrigo                  |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Renal and urinary disorders |               |                |               |
| Anuria                      |               |                |               |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| Bladder pain                |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Dysuria                     |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Glycosuria                  |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0             | 0              | 1              |
| Haematuria                  |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all)           | 0             | 0              | 3              |
| Leukocyturia                |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Micturition disorder        |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Nephropathy                 |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Nocturia                    |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Pollakiuria                 |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Proteinuria                 |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Renal atrophy               |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Renal cyst                  |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Renal pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Urethral haemorrhage<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Urethral pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>1 | 1 / 45 (2.22%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)  | 1 / 4 (25.00%)<br>1 | 1 / 45 (2.22%)<br>2 | 0 / 3 (0.00%)<br>0  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Incontinence<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Endocrine disorders<br>Adrenal disorder<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Arthritis | 0 / 4 (0.00%)<br>0  | 4 / 45 (8.89%)<br>5 | 1 / 3 (33.33%)<br>1 |

|                             |                |                  |                |
|-----------------------------|----------------|------------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1                | 0              |
| Back pain                   |                |                  |                |
| subjects affected / exposed | 2 / 4 (50.00%) | 10 / 45 (22.22%) | 1 / 3 (33.33%) |
| occurrences (all)           | 2              | 10               | 1              |
| Bone lesion                 |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Bone pain                   |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 45 (4.44%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 2                | 0              |
| Flank pain                  |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1                | 0              |
| Groin pain                  |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Joint swelling              |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 45 (4.44%)   | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 2                | 1              |
| Muscle spasms               |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 3 / 45 (6.67%)   | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 3                | 1              |
| Muscular weakness           |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%)   | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1                | 1              |
| Musculoskeletal pain        |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 45 (4.44%)   | 2 / 3 (66.67%) |
| occurrences (all)           | 0              | 2                | 2              |
| Myalgia                     |                |                  |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 45 (4.44%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 2                | 0              |
| Myopathy                    |                |                  |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%)   | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0                | 1              |
| Osteoarthritis              |                |                  |                |

|   |               |                 |               |
|---|---------------|-----------------|---------------|
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Osteolysis                              |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Osteopenia                              |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Osteoporosis                            |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Pain in extremity                       |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 6 / 45 (13.33%) | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 7               | 0             |
| Spinal osteoarthritis                   |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Infections and infestations             |               |                 |               |
| Bacterial infection                     |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Beta haemolytic streptococcal infection |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Bronchitis                              |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Candida infection                       |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Clostridium difficile infection         |               |                 |               |
| subjects affected / exposed             | 0 / 4 (0.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                       | 0             | 0               | 0             |
| Cystitis                                |               |                 |               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Device related infection    |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Diverticulitis              |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Enterococcal infection      |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Erysipelas                  |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Escherichia bacteraemia     |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Escherichia infection       |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Fungal infection            |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Fungal skin infection       |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Fusobacterium infection     |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Gingivitis                  |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Herpes simplex              |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Herpes virus infection      |                |                |                |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Herpes zoster               |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Micrococcus infection       |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Nail bed infection          |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Nasopharyngitis             |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 45 (4.44%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0             | 2              | 1              |
| Oral candidiasis            |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Oral herpes                 |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Pharyngitis                 |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Pneumonia                   |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Pneumonia fungal            |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 45 (2.22%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Pseudomonas infection       |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Sepsis                      |               |                |                |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Skin infection              |               |                |                |



|                                    |                |                 |                |
|------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Staphylococcal infection           |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                  | 0              | 0               | 1              |
| Urinary tract infection            |                |                 |                |
| subjects affected / exposed        | 1 / 4 (25.00%) | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 1              | 0               | 0              |
| Urosepsis                          |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Osteomyelitis                      |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Post procedural infection          |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Soft tissue infection              |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Metabolism and nutrition disorders |                |                 |                |
| Acidosis                           |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Alkalosis                          |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0              |
| Decreased appetite                 |                |                 |                |
| subjects affected / exposed        | 2 / 4 (50.00%) | 6 / 45 (13.33%) | 2 / 3 (66.67%) |
| occurrences (all)                  | 2              | 6               | 2              |
| Dehydration                        |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 1 / 45 (2.22%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0              | 1               | 0              |
| Diabetes mellitus                  |                |                 |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 45 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                  | 0              | 0               | 1              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Hypercalcaemia              |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Hypercholesterolaemia       |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Hyperglycaemia              |                |                |                |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 45 (4.44%) | 2 / 3 (66.67%) |
| occurrences (all)           | 1              | 2              | 3              |
| Hyperkalaemia               |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 3              |
| Hypernatraemia              |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1              | 1              |
| Hyperuricaemia              |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 4 / 45 (8.89%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 6              | 0              |
| Hypoalbuminaemia            |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Hypocalcaemia               |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 45 (2.22%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1              | 1              |
| Hypoglycaemia               |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Hypokalaemia                |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 3 / 45 (6.67%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 5              | 1              |
| Hyponatraemia               |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Hypoproteinaemia            |                |                |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 45 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| Iron overload<br>subjects affected / exposed<br>occurrences (all)        | 0 / 4 (0.00%)<br>0 | 1 / 45 (2.22%)<br>1 | 0 / 3 (0.00%)<br>0 |
| Uraemic acidosis<br>subjects affected / exposed<br>occurrences (all)     | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |
| Fluid overload<br>subjects affected / exposed<br>occurrences (all)       | 0 / 4 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>  | Phase I Schedule A.<br>Volasertib 250<br>mg+LDAC | Phase I Schedule A.<br>Volasertib 300<br>mg+LDAC | Phase II Schedule A.<br>Volasertib 350<br>mg+LDAC |
|--|--|--|---|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed  | 5 / 5 (100.00%)                                  | 9 / 9 (100.00%)                                  | 41 / 42 (97.62%)                                  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Chloroma<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0                               | 2 / 9 (22.22%)<br>2                              | 0 / 42 (0.00%)<br>0                               |
| Leukaemia cutis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0                               | 0 / 9 (0.00%)<br>0                               | 2 / 42 (4.76%)<br>2                               |
| Meningioma<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1                              | 0 / 9 (0.00%)<br>0                               | 0 / 42 (0.00%)<br>0                               |
| Neoplasm progression<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0                               | 1 / 9 (11.11%)<br>1                              | 0 / 42 (0.00%)<br>0                               |
| Small intestine carcinoma<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0                               | 1 / 9 (11.11%)<br>1                              | 0 / 42 (0.00%)<br>0                               |
| Vascular disorders<br>Angiopathy<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1                              | 0 / 9 (0.00%)<br>0                               | 0 / 42 (0.00%)<br>0                               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Circulatory collapse        |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Haematoma                   |                |                |                 |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 9 (11.11%) | 2 / 42 (4.76%)  |
| occurrences (all)           | 2              | 1              | 2               |
| Haemorrhage                 |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Hypertension                |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 1              | 0              | 2               |
| Hypertensive crisis         |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0               |
| Hypotension                 |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 7 / 42 (16.67%) |
| occurrences (all)           | 0              | 1              | 7               |
| Infarction                  |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Peripheral coldness         |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Peripheral embolism         |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Thrombophlebitis            |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Varicose vein               |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Lymphoedema                 |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |

|  |                     |                     |                        |
|--|---------------------|---------------------|------------------------|
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1    |
| Surgical and medical procedures  |                     |                     |                        |
| Central venous catheterisation<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0    |
| Nail operation<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 1 / 42 (2.38%)<br>1    |
| General disorders and administration<br>site conditions                            |                     |                     |                        |
| Adverse drug reaction<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0    |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 5 (20.00%)<br>1 | 1 / 9 (11.11%)<br>1 | 10 / 42 (23.81%)<br>15 |
| Calcinosis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0    |
| Catheter site erythema<br>subjects affected / exposed<br>occurrences (all)         | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0    |
| Catheter site oedema<br>subjects affected / exposed<br>occurrences (all)           | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0    |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)               | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0    |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 2 / 9 (22.22%)<br>2 | 4 / 42 (9.52%)<br>4    |
| Chills<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 5 (40.00%)<br>2 | 1 / 9 (11.11%)<br>1 | 2 / 42 (4.76%)<br>2    |
| Fatigue  |                     |                     |                        |

|                                       |                 |                |                  |
|---------------------------------------|-----------------|----------------|------------------|
| subjects affected / exposed           | 5 / 5 (100.00%) | 5 / 9 (55.56%) | 11 / 42 (26.19%) |
| occurrences (all)                     | 10              | 6              | 11               |
| Feeling cold                          |                 |                |                  |
| subjects affected / exposed           | 0 / 5 (0.00%)   | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                     | 0               | 1              | 0                |
| Feeling hot                           |                 |                |                  |
| subjects affected / exposed           | 1 / 5 (20.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                     | 1               | 0              | 0                |
| Feeling of body temperature change    |                 |                |                  |
| subjects affected / exposed           | 0 / 5 (0.00%)   | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                     | 0               | 0              | 0                |
| Gait disturbance                      |                 |                |                  |
| subjects affected / exposed           | 1 / 5 (20.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                     | 1               | 0              | 0                |
| General physical health deterioration |                 |                |                  |
| subjects affected / exposed           | 2 / 5 (40.00%)  | 1 / 9 (11.11%) | 5 / 42 (11.90%)  |
| occurrences (all)                     | 3               | 1              | 6                |
| Granuloma                             |                 |                |                  |
| subjects affected / exposed           | 1 / 5 (20.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                     | 1               | 0              | 0                |
| Induration                            |                 |                |                  |
| subjects affected / exposed           | 0 / 5 (0.00%)   | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                     | 0               | 1              | 0                |
| Inflammation                          |                 |                |                  |
| subjects affected / exposed           | 0 / 5 (0.00%)   | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)                     | 0               | 0              | 1                |
| Influenza like illness                |                 |                |                  |
| subjects affected / exposed           | 1 / 5 (20.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)                     | 1               | 0              | 1                |
| Infusion site pain                    |                 |                |                  |
| subjects affected / exposed           | 0 / 5 (0.00%)   | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                     | 0               | 1              | 0                |
| Injection site haematoma              |                 |                |                  |
| subjects affected / exposed           | 0 / 5 (0.00%)   | 1 / 9 (11.11%) | 3 / 42 (7.14%)   |
| occurrences (all)                     | 0               | 1              | 3                |
| Injection site reaction               |                 |                |                  |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Local swelling              |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Localised oedema            |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Malaise                     |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)   |
| occurrences (all)           | 0              | 0              | 2                |
| Mucosal inflammation        |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 9 (22.22%) | 10 / 42 (23.81%) |
| occurrences (all)           | 1              | 2              | 12               |
| Oedema                      |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 2 / 42 (4.76%)   |
| occurrences (all)           | 0              | 1              | 2                |
| Oedema mucosal              |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Oedema peripheral           |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 5 / 9 (55.56%) | 12 / 42 (28.57%) |
| occurrences (all)           | 1              | 8              | 16               |
| Pain                        |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 5 / 42 (11.90%)  |
| occurrences (all)           | 0              | 2              | 5                |
| Puncture site pain          |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Pyrexia                     |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 4 / 9 (44.44%) | 13 / 42 (30.95%) |
| occurrences (all)           | 1              | 10             | 18               |
| Thirst decreased            |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 1              | 0              | 0                |
| Peripheral swelling         |                |                |                  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed              | 1 / 5 (20.00%) | 2 / 9 (22.22%) | 2 / 42 (4.76%) |
| occurrences (all)                        | 1              | 4              | 2              |
| Catheter site pain                       |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Hyperthermia                             |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                        | 0              | 0              | 1              |
| Discomfort                               |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Mucosal haemorrhage                      |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                        | 0              | 0              | 4              |
| Social circumstances                     |                |                |                |
| Fasting                                  |                |                |                |
| subjects affected / exposed              | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0              |
| Reproductive system and breast disorders |                |                |                |
| Breast enlargement                       |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Genital swelling                         |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Haematospermia                           |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Nipple disorder                          |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Pelvic pain                              |                |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0              |
| Penile oedema                            |                |                |                |



|   |                |                |                  |
|---|----------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |
| Scrotal oedema                                  |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |
| Vaginal haemorrhage                             |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                               | 0              | 0              | 0                |
| Vulvovaginal erythema                           |                |                |                  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                               | 1              | 0              | 0                |
| Genital burning sensation                       |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                               | 0              | 0              | 0                |
| Respiratory, thoracic and mediastinal disorders |                |                |                  |
| Atelectasis                                     |                |                |                  |
| subjects affected / exposed                     | 2 / 5 (40.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                               | 2              | 1              | 0                |
| Bronchial secretion retention                   |                |                |                  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                               | 1              | 0              | 0                |
| Dysphonia                                       |                |                |                  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                               | 1              | 1              | 0                |
| Cough   |                |                |                  |
| subjects affected / exposed                     | 2 / 5 (40.00%) | 4 / 9 (44.44%) | 10 / 42 (23.81%) |
| occurrences (all)                               | 2              | 4              | 18               |
| Dyspnoea  |                |                |                  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 4 / 9 (44.44%) | 10 / 42 (23.81%) |
| occurrences (all)                               | 0              | 5              | 12               |
| Dyspnoea exertional                             |                |                |                  |
| subjects affected / exposed                     | 3 / 5 (60.00%) | 2 / 9 (22.22%) | 0 / 42 (0.00%)   |
| occurrences (all)                               | 4              | 2              | 0                |
| Haemoptysis                                     |                |                |                  |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 5 / 42 (11.90%)  |
| occurrences (all)           | 0              | 2              | 6                |
| Epistaxis                   |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 3 / 9 (33.33%) | 16 / 42 (38.10%) |
| occurrences (all)           | 1              | 7              | 24               |
| Hiccups                     |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Laryngeal disorder          |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Lung infiltration           |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 9 (22.22%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 2              | 0                |
| Lung disorder               |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Nasal inflammation          |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Oropharyngeal pain          |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 5 / 42 (11.90%)  |
| occurrences (all)           | 0              | 1              | 5                |
| Pharyngeal inflammation     |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Pleural effusion            |                |                |                  |
| subjects affected / exposed | 2 / 5 (40.00%) | 4 / 9 (44.44%) | 3 / 42 (7.14%)   |
| occurrences (all)           | 2              | 4              | 3                |
| Productive cough            |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)           | 0              | 0              | 1                |
| Pulmonary hypertension      |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Respiratory failure         |                |                |                  |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Sputum discoloured          |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Sputum retention            |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Vocal cord disorder         |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Rales                       |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Rhonchi                     |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Throat irritation           |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Psychiatric disorders       |                |                |                 |
| Agitation                   |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Anxiety                     |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 5 / 42 (11.90%) |
| occurrences (all)           | 1              | 1              | 5               |
| Communication disorder      |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Confusional state           |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 2 / 42 (4.76%)  |
| occurrences (all)           | 1              | 1              | 2               |
| Depressed mood              |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0               |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Disorientation                                  |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Hallucination                                   |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)                               | 0              | 0              | 2              |
| Hallucination, visual                           |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Initial insomnia                                |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Insomnia  |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%) |
| occurrences (all)                               | 0              | 0              | 3              |
| Panic attack                                    |                |                |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                               | 1              | 0              | 3              |
| Restlessness                                    |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                               | 0              | 0              | 2              |
| Sleep disorder                                  |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%) |
| occurrences (all)                               | 0              | 0              | 3              |
| Suicidal ideation                               |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Investigations                                  |                |                |                |
| Activated partial thromboplastin time prolonged |                |                |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Activated partial thromboplastin time shortened |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Alanine aminotransferase increased     |                |                |                |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 2              | 0              | 0              |
| Aspartate aminotransferase increased   |                |                |                |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Blast cell count increased             |                |                |                |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Blood albumin decreased                |                |                |                |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood albumin increased                |                |                |                |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Blood alkaline phosphatase increased   |                |                |                |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                      | 1              | 0              | 3              |
| Blood bilirubin increased              |                |                |                |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Blood chloride increased               |                |                |                |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Blood creatine phosphokinase decreased |                |                |                |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood creatine phosphokinase increased |                |                |                |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Blood creatinine                       |                |                |                |

|                                       |                |                |                |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed           | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 1              | 0              | 0              |
| Blood creatinine decreased            |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 2 / 9 (22.22%) | 0 / 42 (0.00%) |
| occurrences (all)                     | 0              | 4              | 0              |
| Blood creatinine increased            |                |                |                |
| subjects affected / exposed           | 1 / 5 (20.00%) | 3 / 9 (33.33%) | 2 / 42 (4.76%) |
| occurrences (all)                     | 3              | 4              | 2              |
| Blood fibrinogen increased            |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood glucose increased               |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood iron decreased                  |                |                |                |
| subjects affected / exposed           | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 1              | 0              | 0              |
| Blood iron increased                  |                |                |                |
| subjects affected / exposed           | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 1              | 0              | 0              |
| Blood lactate dehydrogenase decreased |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Blood lactate dehydrogenase increased |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood phosphorus decreased            |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                     | 0              | 0              | 0              |
| Blood potassium decreased             |                |                |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)                     | 0              | 0              | 2              |
| Blood pressure increased              |                |                |                |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed    | 2 / 5 (40.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)              | 2              | 0              | 0              |
| Blood triglycerides increased  |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Blood urea decreased           |                |                |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Blood urea increased           |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 2 / 9 (22.22%) | 0 / 42 (0.00%) |
| occurrences (all)              | 2              | 2              | 0              |
| Blood uric acid increased      |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)              | 1              | 1              | 0              |
| Blood urine present            |                |                |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)              | 0              | 1              | 1              |
| Body temperature increased     |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Breath sounds abnormal         |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| C-reactive protein increased   |                |                |                |
| subjects affected / exposed    | 2 / 5 (40.00%) | 4 / 9 (44.44%) | 2 / 42 (4.76%) |
| occurrences (all)              | 3              | 4              | 2              |
| Candida test positive          |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)              | 1              | 0              | 0              |
| Ejection fraction decreased    |                |                |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)              | 1              | 1              | 0              |
| Electrocardiogram QT prolonged |                |                |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)              | 0              | 0              | 1              |
| Electrocardiogram change       |                |                |                |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Enterococcus test positive           |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Escherichia test positive            |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 1              | 0              | 0              |
| Gamma-glutamyltransferase increased  |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)                    | 1              | 1              | 1              |
| Heart rate increased                 |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Hepatic enzyme increased             |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Liver function test abnormal         |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Oxygen saturation decreased          |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Prostatic specific antigen increased |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Protein total decreased              |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Prothrombin time prolonged           |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                    | 1              | 1              | 0              |
| Serum ferritin increased             |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Thrombin time shortened<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Troponin increased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 2 / 42 (4.76%)<br>3 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>2 | 1 / 42 (2.38%)<br>1 |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| International normalised ratio increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Allergic transfusion reaction<br>subjects affected / exposed<br>occurrences (all)            | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Drug administration error<br>subjects affected / exposed<br>occurrences (all)                | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0 |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 5 (20.00%)<br>2 | 4 / 9 (44.44%)<br>4 | 4 / 42 (9.52%)<br>4 |
| Laceration   |                     |                     |                     |

|                                  |                |                |                |
|----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed      | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 1              | 0              |
| Lip injury                       |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Procedural pain                  |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)                | 0              | 1              | 1              |
| Transfusion reaction             |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Wound                            |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)                | 0              | 1              | 1              |
| Skin abrasion                    |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 1              | 0              |
| Stoma site haemorrhage           |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Cardiac disorders                |                |                |                |
| Angina pectoris                  |                |                |                |
| subjects affected / exposed      | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)                | 1              | 0              | 2              |
| Aortic valve incompetence        |                |                |                |
| subjects affected / exposed      | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                | 1              | 0              | 0              |
| Arteriosclerosis coronary artery |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |
| Atrioventricular block           |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                | 0              | 0              | 1              |
| Bradycardia                      |                |                |                |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                | 0              | 0              | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Bundle branch block right<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Cardiac arrest<br>subjects affected / exposed<br>occurrences (all)             | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Cardiac disorder<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0 |
| Cardiac failure<br>subjects affected / exposed<br>occurrences (all)            | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 2 / 42 (4.76%)<br>3 |
| Cardiac valve disease<br>subjects affected / exposed<br>occurrences (all)      | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Cardiomegaly<br>subjects affected / exposed<br>occurrences (all)               | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Cardiomyopathy<br>subjects affected / exposed<br>occurrences (all)             | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Cardiovascular disorder<br>subjects affected / exposed<br>occurrences (all)    | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0 |
| Congestive cardiomyopathy<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Extrasystoles<br>subjects affected / exposed<br>occurrences (all)              | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Heart valve incompetence<br>subjects affected / exposed<br>occurrences (all)   | 2 / 5 (40.00%)<br>2 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Hypertensive heart disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Left ventricular hypertrophy<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0 |
| Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 42 (2.38%)<br>2 |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 5 (20.00%)<br>1 | 2 / 9 (22.22%)<br>2 | 0 / 42 (0.00%)<br>0 |
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 1 / 42 (2.38%)<br>1 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>2 | 1 / 42 (2.38%)<br>1 |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1 |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0 |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1 |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 42 (2.38%)<br>2 |
| Nervous system disorders<br>Burning sensation<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0 |
| Dizziness   |                     |                     |                     |

|                               |                |                |                |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed   | 4 / 5 (80.00%) | 2 / 9 (22.22%) | 3 / 42 (7.14%) |
| occurrences (all)             | 4              | 2              | 6              |
| Headache                      |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 4 / 42 (9.52%) |
| occurrences (all)             | 0              | 0              | 6              |
| Hemiparesis                   |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Orthostatic intolerance       |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Paraesthesia                  |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)             | 0              | 0              | 1              |
| Peripheral sensory neuropathy |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Polyneuropathy                |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Sinus headache                |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Somnolence                    |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)             | 0              | 1              | 1              |
| Syncope                       |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 1              | 0              |
| Tremor                        |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)             | 0              | 0              | 1              |
| Ageusia                       |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Dysgeusia                     |                |                |                |

|                                      |                |                |                  |
|--------------------------------------|----------------|----------------|------------------|
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Hypotonia                            |                |                |                  |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Blood and lymphatic system disorders |                |                |                  |
| Anaemia                              |                |                |                  |
| subjects affected / exposed          | 4 / 5 (80.00%) | 6 / 9 (66.67%) | 14 / 42 (33.33%) |
| occurrences (all)                    | 5              | 20             | 27               |
| Febrile neutropenia                  |                |                |                  |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 8 / 42 (19.05%)  |
| occurrences (all)                    | 0              | 2              | 9                |
| Leukocytosis                         |                |                |                  |
| subjects affected / exposed          | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)                    | 1              | 1              | 0                |
| Leukopenia                           |                |                |                  |
| subjects affected / exposed          | 2 / 5 (40.00%) | 5 / 9 (55.56%) | 1 / 42 (2.38%)   |
| occurrences (all)                    | 3              | 9              | 1                |
| Lymphadenopathy                      |                |                |                  |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)                    | 1              | 0              | 1                |
| Neutropenia                          |                |                |                  |
| subjects affected / exposed          | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 11 / 42 (26.19%) |
| occurrences (all)                    | 1              | 1              | 36               |
| Splenomegaly                         |                |                |                  |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 2 / 9 (22.22%) | 0 / 42 (0.00%)   |
| occurrences (all)                    | 0              | 2              | 0                |
| Thrombocytopenia                     |                |                |                  |
| subjects affected / exposed          | 4 / 5 (80.00%) | 5 / 9 (55.56%) | 9 / 42 (21.43%)  |
| occurrences (all)                    | 5              | 16             | 45               |
| Cytopenia                            |                |                |                  |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Ear and labyrinth disorders          |                |                |                  |
| Ear haemorrhage                      |                |                |                  |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Vertigo                     |                |                |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 3 / 42 (7.14%) |
| occurrences (all)           | 2              | 2              | 3              |
| Eye disorders               |                |                |                |
| Cataract                    |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dry eye                     |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Erythema of eyelid          |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Eye haemorrhage             |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)           | 0              | 0              | 3              |
| Eyelid oedema               |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Glaucoma                    |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Lacrimation increased       |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Macular degeneration        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Visual acuity reduced       |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Visual impairment           |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| Hyphaema                    |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Photopsia                   |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Gastrointestinal disorders  |                |                |                  |
| Abdominal pain              |                |                |                  |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 4 / 42 (9.52%)   |
| occurrences (all)           | 2              | 3              | 4                |
| Abdominal pain upper        |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 3 / 42 (7.14%)   |
| occurrences (all)           | 0              | 1              | 4                |
| Abnormal faeces             |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Anal haemorrhage            |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)           | 0              | 0              | 1                |
| Ascites                     |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Constipation                |                |                |                  |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 18 / 42 (42.86%) |
| occurrences (all)           | 3              | 2              | 26               |
| Diarrhoea                   |                |                |                  |
| subjects affected / exposed | 2 / 5 (40.00%) | 4 / 9 (44.44%) | 13 / 42 (30.95%) |
| occurrences (all)           | 7              | 7              | 21               |
| Dry mouth                   |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 9 (22.22%) | 2 / 42 (4.76%)   |
| occurrences (all)           | 0              | 2              | 2                |
| Dyspepsia                   |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%)   |
| occurrences (all)           | 0              | 0              | 3                |
| Dysphagia                   |                |                |                  |



|                               |                |                |                |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 3 / 42 (7.14%) |
| occurrences (all)             | 0              | 1              | 3              |
| Enterocolitis                 |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Faecaloma                     |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Flatulence                    |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Gastritis                     |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Gastrointestinal inflammation |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Gingival bleeding             |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)             | 1              | 2              | 1              |
| Gingival discolouration       |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 1              | 0              | 0              |
| Gingival pain                 |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)             | 1              | 0              | 1              |
| Gingival swelling             |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Glossodynia                   |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 2              | 0              |
| Haematochezia                 |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)             | 0              | 0              | 0              |
| Haemorrhoids                  |                |                |                |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Hiatus hernia               |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)           | 1              | 0              | 1                |
| Mouth haemorrhage           |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)   |
| occurrences (all)           | 0              | 0              | 2                |
| Mouth ulceration            |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 2 / 42 (4.76%)   |
| occurrences (all)           | 0              | 1              | 2                |
| Nausea                      |                |                |                  |
| subjects affected / exposed | 2 / 5 (40.00%) | 4 / 9 (44.44%) | 19 / 42 (45.24%) |
| occurrences (all)           | 5              | 6              | 28               |
| Oesophagitis                |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Oral mucosal erythema       |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Oral pain                   |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%)   |
| occurrences (all)           | 0              | 0              | 3                |
| Periodontal disease         |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Proctalgia                  |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)           | 0              | 0              | 1                |
| Rectal haemorrhage          |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 1              | 0              | 0                |
| Small intestine ulcer       |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 1              | 0              | 0                |
| Stomatitis                  |                |                |                  |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)   |
| occurrences (all)           | 0              | 0              | 3                |
| Tongue coated               |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 1              | 1              | 0                |
| Tongue ulceration           |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 2              | 0                |
| Toothache                   |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Vomiting                    |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 4 / 9 (44.44%) | 16 / 42 (38.10%) |
| occurrences (all)           | 2              | 5              | 30               |
| Anal incontinence           |                |                |                  |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 1              | 0              | 0                |
| Aphthous ulcer              |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%)   |
| occurrences (all)           | 0              | 0              | 4                |
| Tongue discolouration       |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 1              | 0                |
| Abdominal discomfort        |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Gastric ulcer               |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Gastrointestinal disorder   |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)           | 0              | 0              | 1                |
| Palatal disorder            |                |                |                  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)           | 0              | 0              | 1                |
| Tongue haemorrhage          |                |                |                  |

|  |                    |                    |                     |
|--|--------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 9 (0.00%)<br>0 | 0 / 42 (0.00%)<br>0 |
| Hepatobiliary disorders                          |                    |                    |                     |
| Cholelithiasis                                   |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 9 (0.00%)      | 0 / 42 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Hepatic congestion                               |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 9 (0.00%)      | 0 / 42 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Hepatic cyst                                     |                    |                    |                     |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 1 / 9 (11.11%)     | 0 / 42 (0.00%)      |
| occurrences (all)                                | 1                  | 1                  | 0                   |
| Hepatic lesion                                   |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 1 / 9 (11.11%)     | 0 / 42 (0.00%)      |
| occurrences (all)                                | 0                  | 1                  | 0                   |
| Hepatomegaly                                     |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 9 (0.00%)      | 0 / 42 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Hyperbilirubinaemia                              |                    |                    |                     |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 0 / 9 (0.00%)      | 0 / 42 (0.00%)      |
| occurrences (all)                                | 1                  | 0                  | 0                   |
| Hepatic steatosis                                |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 9 (0.00%)      | 0 / 42 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Skin and subcutaneous tissue disorders           |                    |                    |                     |
| Alopecia   |                    |                    |                     |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 0 / 9 (0.00%)      | 3 / 42 (7.14%)      |
| occurrences (all)                                | 1                  | 0                  | 5                   |
| Blister  |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 1 / 9 (11.11%)     | 0 / 42 (0.00%)      |
| occurrences (all)                                | 0                  | 1                  | 0                   |
| Blood blister                                    |                    |                    |                     |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 9 (0.00%)      | 1 / 42 (2.38%)      |
| occurrences (all)                                | 0                  | 0                  | 1                   |
| Dermatitis atopic                                |                    |                    |                     |

|                                 |                |                |                  |
|---------------------------------|----------------|----------------|------------------|
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)               | 0              | 0              | 0                |
| <b>Dermatitis exfoliative</b>   |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)               | 0              | 1              | 0                |
| <b>Dry skin</b>                 |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 3 / 9 (33.33%) | 2 / 42 (4.76%)   |
| occurrences (all)               | 0              | 3              | 2                |
| <b>Erythema</b>                 |                |                |                  |
| subjects affected / exposed     | 2 / 5 (40.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%)   |
| occurrences (all)               | 2              | 1              | 1                |
| <b>Haemorrhage subcutaneous</b> |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)               | 0              | 0              | 0                |
| <b>Hyperhidrosis</b>            |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 3 / 42 (7.14%)   |
| occurrences (all)               | 0              | 1              | 3                |
| <b>Night sweats</b>             |                |                |                  |
| subjects affected / exposed     | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 4 / 42 (9.52%)   |
| occurrences (all)               | 1              | 0              | 5                |
| <b>Pain of skin</b>             |                |                |                  |
| subjects affected / exposed     | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%)   |
| occurrences (all)               | 1              | 0              | 1                |
| <b>Parapsoriasis</b>            |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)   |
| occurrences (all)               | 0              | 1              | 0                |
| <b>Petechiae</b>                |                |                |                  |
| subjects affected / exposed     | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 10 / 42 (23.81%) |
| occurrences (all)               | 4              | 2              | 12               |
| <b>Pruritus</b>                 |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 4 / 42 (9.52%)   |
| occurrences (all)               | 0              | 0              | 5                |
| <b>Psoriasis</b>                |                |                |                  |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)   |
| occurrences (all)               | 0              | 0              | 0                |
| <b>Purpura</b>                  |                |                |                  |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%) |
| occurrences (all)           | 0              | 0              | 3              |
| Rash                        |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 3 / 42 (7.14%) |
| occurrences (all)           | 1              | 0              | 3              |
| Skin erosion                |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Skin haemorrhage            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Skin hyperpigmentation      |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)           | 0              | 1              | 1              |
| Skin lesion                 |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 2 / 42 (4.76%) |
| occurrences (all)           | 1              | 1              | 2              |
| Swelling face               |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Urticaria                   |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)           | 1              | 0              | 1              |
| Eczema                      |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Ingrowing nail              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Intertrigo                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Renal and urinary disorders |                |                |                |
| Anuria                      |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Bladder pain                |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Dysuria                     |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 3 / 42 (7.14%) |
| occurrences (all)           | 1              | 2              | 3              |
| Glycosuria                  |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Haematuria                  |                |                |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 1 / 42 (2.38%) |
| occurrences (all)           | 2              | 2              | 1              |
| Leukocyturia                |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Micturition disorder        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Nephropathy                 |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Nocturia                    |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Pollakiuria                 |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Proteinuria                 |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Renal atrophy               |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Renal cyst                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)           | 0              | 1              | 1              |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 1 / 42 (2.38%)<br>1  |
| Renal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0  |
| Urethral haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1 | 1 / 9 (11.11%)<br>1 | 0 / 42 (0.00%)<br>0  |
| Urethral pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 2 / 5 (40.00%)<br>2 | 1 / 9 (11.11%)<br>1 | 1 / 42 (2.38%)<br>1  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Endocrine disorders<br>Adrenal disorder<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 5 (20.00%)<br>1 | 0 / 9 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 3 / 9 (33.33%)<br>3 | 7 / 42 (16.67%)<br>9 |
| Arthritis   |                     |                     |                      |



|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 0              | 0              | 4               |
| Back pain                   |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 9 (22.22%) | 6 / 42 (14.29%) |
| occurrences (all)           | 1              | 2              | 6               |
| Bone lesion                 |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Bone pain                   |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Flank pain                  |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Groin pain                  |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Joint swelling              |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Muscle spasms               |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 2              | 0              | 3               |
| Muscular weakness           |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%)  |
| occurrences (all)           | 1              | 2              | 1               |
| Musculoskeletal pain        |                |                |                 |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 9 (11.11%) | 2 / 42 (4.76%)  |
| occurrences (all)           | 2              | 1              | 2               |
| Myalgia                     |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%)  |
| occurrences (all)           | 0              | 0              | 3               |
| Myopathy                    |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Osteoarthritis              |                |                |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0              |
| Osteolysis                              |                |                |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Osteopenia                              |                |                |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0              |
| Osteoporosis                            |                |                |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0              |
| Pain in extremity                       |                |                |                |
| subjects affected / exposed             | 2 / 5 (40.00%) | 3 / 9 (33.33%) | 3 / 42 (7.14%) |
| occurrences (all)                       | 3              | 4              | 7              |
| Spinal osteoarthritis                   |                |                |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Infections and infestations             |                |                |                |
| Bacterial infection                     |                |                |                |
| subjects affected / exposed             | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Beta haemolytic streptococcal infection |                |                |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0              |
| Bronchitis                              |                |                |                |
| subjects affected / exposed             | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)                       | 1              | 0              | 3              |
| Candida infection                       |                |                |                |
| subjects affected / exposed             | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)                       | 1              | 0              | 1              |
| Clostridium difficile infection         |                |                |                |
| subjects affected / exposed             | 2 / 5 (40.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)                       | 2              | 0              | 2              |
| Cystitis                                |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Device related infection    |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Diverticulitis              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Enterococcal infection      |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 1 / 42 (2.38%) |
| occurrences (all)           | 1              | 1              | 1              |
| Erysipelas                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Escherichia bacteraemia     |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Escherichia infection       |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Fungal infection            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 2 / 42 (4.76%) |
| occurrences (all)           | 0              | 1              | 2              |
| Fungal skin infection       |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Fusobacterium infection     |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gingivitis                  |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 1 / 42 (2.38%) |
| occurrences (all)           | 1              | 0              | 1              |
| Herpes simplex              |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%) |
| occurrences (all)           | 2              | 0              | 2              |
| Herpes virus infection      |                |                |                |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Herpes zoster               |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Micrococcus infection       |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Nail bed infection          |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Nasopharyngitis             |                |                |                 |
| subjects affected / exposed | 2 / 5 (40.00%) | 4 / 9 (44.44%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 2              | 4              | 0               |
| Oral candidiasis            |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 9 (11.11%) | 2 / 42 (4.76%)  |
| occurrences (all)           | 1              | 1              | 2               |
| Oral herpes                 |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Pharyngitis                 |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Pneumonia                   |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 5 / 42 (11.90%) |
| occurrences (all)           | 1              | 0              | 5               |
| Pneumonia fungal            |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Pseudomonas infection       |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Sepsis                      |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 1 / 42 (2.38%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Skin infection              |                |                |                 |

|                                    |                |                |                 |
|------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Staphylococcal infection           |                |                |                 |
| subjects affected / exposed        | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Urinary tract infection            |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 3 / 42 (7.14%)  |
| occurrences (all)                  | 0              | 0              | 3               |
| Urosepsis                          |                |                |                 |
| subjects affected / exposed        | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Osteomyelitis                      |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Post procedural infection          |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Soft tissue infection              |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Metabolism and nutrition disorders |                |                |                 |
| Acidosis                           |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Alkalosis                          |                |                |                 |
| subjects affected / exposed        | 2 / 5 (40.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)                  | 3              | 2              | 0               |
| Decreased appetite                 |                |                |                 |
| subjects affected / exposed        | 4 / 5 (80.00%) | 5 / 9 (55.56%) | 6 / 42 (14.29%) |
| occurrences (all)                  | 5              | 6              | 10              |
| Dehydration                        |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 1 / 42 (2.38%)  |
| occurrences (all)                  | 0              | 1              | 1               |
| Diabetes mellitus                  |                |                |                 |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Hypercalcaemia              |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Hypercholesterolaemia       |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Hyperglycaemia              |                |                |                 |
| subjects affected / exposed | 4 / 5 (80.00%) | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 8              | 1              | 0               |
| Hyperkalaemia               |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 3 / 42 (7.14%)  |
| occurrences (all)           | 1              | 0              | 6               |
| Hypernatraemia              |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Hyperuricaemia              |                |                |                 |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 9 (22.22%) | 1 / 42 (2.38%)  |
| occurrences (all)           | 2              | 4              | 6               |
| Hypoalbuminaemia            |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 9 (11.11%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Hypocalcaemia               |                |                |                 |
| subjects affected / exposed | 3 / 5 (60.00%) | 2 / 9 (22.22%) | 2 / 42 (4.76%)  |
| occurrences (all)           | 3              | 5              | 2               |
| Hypoglycaemia               |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 9 (0.00%)  | 2 / 42 (4.76%)  |
| occurrences (all)           | 1              | 0              | 2               |
| Hypokalaemia                |                |                |                 |
| subjects affected / exposed | 4 / 5 (80.00%) | 4 / 9 (44.44%) | 8 / 42 (19.05%) |
| occurrences (all)           | 5              | 6              | 11              |
| Hyponatraemia               |                |                |                 |
| subjects affected / exposed | 3 / 5 (60.00%) | 4 / 9 (44.44%) | 0 / 42 (0.00%)  |
| occurrences (all)           | 4              | 4              | 0               |
| Hypoproteinaemia            |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 9 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |

|                             |               |               |                |
|-----------------------------|---------------|---------------|----------------|
| Iron overload               |               |               |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0             | 0             | 0              |
| Uraemic acidosis            |               |               |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0             | 0             | 0              |
| Vitamin D deficiency        |               |               |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0             | 0             | 0              |
| Fluid overload              |               |               |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 9 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all)           | 0             | 0             | 0              |

| <b>Non-serious adverse events</b>                                   | Phase I Schedule A.<br>Volasertib 350<br>mg+LDAC | Phase I Schedule A.<br>Volasertib 400<br>mg+LDAC | Phase I Schedule B.<br>Volasertib 400 mg |
|---|--|--|--|
| Total subjects affected by non-serious adverse events               |  |  |  |
| subjects affected / exposed   | 8 / 8 (100.00%)                                  | 3 / 3 (100.00%)                                  | 6 / 6 (100.00%)                          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Chloroma  |  |  |  |
| subjects affected / exposed   | 0 / 8 (0.00%)                                    | 0 / 3 (0.00%)                                    | 1 / 6 (16.67%)                           |
| occurrences (all)   | 0  | 0  | 1  |
| Leukaemia cutis   |  |  |  |
| subjects affected / exposed   | 0 / 8 (0.00%)                                    | 0 / 3 (0.00%)                                    | 0 / 6 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Meningioma  |  |  |  |
| subjects affected / exposed   | 0 / 8 (0.00%)                                    | 0 / 3 (0.00%)                                    | 0 / 6 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Neoplasm progression  |  |  |  |
| subjects affected / exposed   | 0 / 8 (0.00%)                                    | 0 / 3 (0.00%)                                    | 0 / 6 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Small intestine carcinoma   |  |  |  |
| subjects affected / exposed   | 0 / 8 (0.00%)                                    | 0 / 3 (0.00%)                                    | 0 / 6 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Vascular disorders  |  |  |  |
| Angiopathy  |  |  |  |
| subjects affected / exposed   | 0 / 8 (0.00%)                                    | 0 / 3 (0.00%)                                    | 0 / 6 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Circulatory collapse        |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Haematoma                   |                |                |                |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 3 (0.00%)  | 3 / 6 (50.00%) |
| occurrences (all)           | 3              | 0              | 4              |
| Haemorrhage                 |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Hypertension                |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Hypertensive crisis         |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Hypotension                 |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Infarction                  |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Peripheral coldness         |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Peripheral embolism         |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Thrombophlebitis            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Varicose vein               |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Lymphoedema                 |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Surgical and medical procedures  |                     |                     |                     |
| Central venous catheterisation<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Nail operation<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| General disorders and administration<br>site conditions                            |                     |                     |                     |
| Adverse drug reaction<br>subjects affected / exposed<br>occurrences (all)          | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Calcinosis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Catheter site erythema<br>subjects affected / exposed<br>occurrences (all)         | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Catheter site oedema<br>subjects affected / exposed<br>occurrences (all)           | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)               | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 8 (37.50%)<br>3 | 2 / 3 (66.67%)<br>2 | 0 / 6 (0.00%)<br>0  |
| Fatigue  |                     |                     |                     |

|                                       |                |                |                |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed           | 4 / 8 (50.00%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 5              | 1              | 0              |
| Feeling cold                          |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Feeling hot                           |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                     | 0              | 0              | 1              |
| Feeling of body temperature change    |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Gait disturbance                      |                |                |                |
| subjects affected / exposed           | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0              |
| General physical health deterioration |                |                |                |
| subjects affected / exposed           | 3 / 8 (37.50%) | 1 / 3 (33.33%) | 2 / 6 (33.33%) |
| occurrences (all)                     | 6              | 1              | 2              |
| Granuloma                             |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Induration                            |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Inflammation                          |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 1              | 0              |
| Influenza like illness                |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Infusion site pain                    |                |                |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0              | 0              |
| Injection site haematoma              |                |                |                |
| subjects affected / exposed           | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0              |
| Injection site reaction               |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Local swelling              |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Localised oedema            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Malaise                     |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Mucosal inflammation        |                |                |                |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 3 (0.00%)  | 2 / 6 (33.33%) |
| occurrences (all)           | 3              | 0              | 2              |
| Oedema                      |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Oedema mucosal              |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Oedema peripheral           |                |                |                |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 3 (33.33%) | 1 / 6 (16.67%) |
| occurrences (all)           | 5              | 1              | 1              |
| Pain                        |                |                |                |
| subjects affected / exposed | 3 / 8 (37.50%) | 1 / 3 (33.33%) | 1 / 6 (16.67%) |
| occurrences (all)           | 3              | 1              | 1              |
| Puncture site pain          |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Pyrexia                     |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Thirst decreased            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Peripheral swelling         |                |                |                |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed              | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0             |
| Catheter site pain                       |                |                |               |
| subjects affected / exposed              | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0             |
| Hyperthermia                             |                |                |               |
| subjects affected / exposed              | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0             |
| Discomfort                               |                |                |               |
| subjects affected / exposed              | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0             |
| Mucosal haemorrhage                      |                |                |               |
| subjects affected / exposed              | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0             |
| Social circumstances                     |                |                |               |
| Fasting                                  |                |                |               |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Reproductive system and breast disorders |                |                |               |
| Breast enlargement                       |                |                |               |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Genital swelling                         |                |                |               |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Haematospermia                           |                |                |               |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Nipple disorder                          |                |                |               |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Pelvic pain                              |                |                |               |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                        | 0              | 0              | 0             |
| Penile oedema                            |                |                |               |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Scrotal oedema                                  |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Vaginal haemorrhage                             |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Vulvovaginal erythema                           |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Genital burning sensation                       |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0              |
| Respiratory, thoracic and mediastinal disorders |                |               |                |
| Atelectasis                                     |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Bronchial secretion retention                   |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Dysphonia                                       |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Cough   |                |               |                |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                               | 2              | 0             | 1              |
| Dyspnoea  |                |               |                |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 0 / 3 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all)                               | 2              | 0             | 2              |
| Dyspnoea exertional                             |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                               | 1              | 0             | 1              |
| Haemoptysis                                     |                |               |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Epistaxis                   |                |                |                |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 2 / 6 (33.33%) |
| occurrences (all)           | 2              | 0              | 5              |
| Hiccups                     |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Laryngeal disorder          |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Lung infiltration           |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 1              | 1              |
| Lung disorder               |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nasal inflammation          |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Oropharyngeal pain          |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Pharyngeal inflammation     |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Pleural effusion            |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Productive cough            |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Pulmonary hypertension      |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Respiratory failure         |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Sputum discoloured          |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Sputum retention            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Vocal cord disorder         |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Rales                       |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Rhonchi                     |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Throat irritation           |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Psychiatric disorders       |                |                |                |
| Agitation                   |                |                |                |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0              |
| Anxiety                     |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 1              | 0              | 1              |
| Communication disorder      |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Confusional state           |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Depressed mood              |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Depression                                      |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Disorientation                                  |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0              |
| Hallucination                                   |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Hallucination, visual                           |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Initial insomnia                                |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                               | 0              | 0             | 1              |
| Insomnia  |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Panic attack                                    |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Restlessness                                    |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                               | 1              | 0             | 1              |
| Sleep disorder                                  |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Suicidal ideation                               |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Investigations                                  |                |               |                |
| Activated partial thromboplastin time prolonged |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Activated partial thromboplastin time shortened |                |               |                |



|  |               |               |                |
|--|---------------|---------------|----------------|
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Alanine aminotransferase increased     |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                      | 0             | 0             | 1              |
| Aspartate aminotransferase increased   |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                      | 0             | 0             | 1              |
| Blast cell count increased             |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Blood albumin decreased                |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Blood albumin increased                |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                      | 0             | 0             | 2              |
| Blood alkaline phosphatase increased   |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Blood bilirubin increased              |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                      | 0             | 0             | 2              |
| Blood chloride increased               |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Blood creatine phosphokinase decreased |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Blood creatine phosphokinase increased |               |               |                |
| subjects affected / exposed            | 0 / 8 (0.00%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0             | 0             | 0              |
| Blood creatinine                       |               |               |                |

|                                       |                |               |                |
|---------------------------------------|----------------|---------------|----------------|
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood creatinine decreased            |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood creatinine increased            |                |               |                |
| subjects affected / exposed           | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all)                     | 1              | 0             | 2              |
| Blood fibrinogen increased            |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood glucose increased               |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood iron decreased                  |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood iron increased                  |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood lactate dehydrogenase decreased |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood lactate dehydrogenase increased |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood phosphorus decreased            |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 0              | 0             | 0              |
| Blood potassium decreased             |                |               |                |
| subjects affected / exposed           | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all)                     | 0              | 0             | 3              |
| Blood pressure increased              |                |               |                |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed    | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 2              | 0              | 0              |
| Blood triglycerides increased  |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Blood urea decreased           |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Blood urea increased           |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 2 / 6 (33.33%) |
| occurrences (all)              | 0              | 0              | 5              |
| Blood uric acid increased      |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)              | 0              | 0              | 3              |
| Blood urine present            |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Body temperature increased     |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Breath sounds abnormal         |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| C-reactive protein increased   |                |                |                |
| subjects affected / exposed    | 4 / 8 (50.00%) | 1 / 3 (33.33%) | 3 / 6 (50.00%) |
| occurrences (all)              | 4              | 1              | 3              |
| Candida test positive          |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Ejection fraction decreased    |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Electrocardiogram QT prolonged |                |                |                |
| subjects affected / exposed    | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)              | 0              | 0              | 0              |
| Electrocardiogram change       |                |                |                |

|                                      |               |                |               |
|--------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Enterococcus test positive           |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 1              | 0             |
| Escherichia test positive            |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Gamma-glutamyltransferase increased  |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Heart rate increased                 |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Hepatic enzyme increased             |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Liver function test abnormal         |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Oxygen saturation decreased          |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 1              | 0             |
| Prostatic specific antigen increased |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Protein total decreased              |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Prothrombin time prolonged           |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Serum ferritin increased             |               |                |               |
| subjects affected / exposed          | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Thrombin time shortened<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Troponin increased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| International normalised ratio increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Allergic transfusion reaction<br>subjects affected / exposed<br>occurrences (all)            | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Drug administration error<br>subjects affected / exposed<br>occurrences (all)                | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 8 (12.50%)<br>1 | 1 / 3 (33.33%)<br>1 | 1 / 6 (16.67%)<br>1 |
| Laceration   |                     |                     |                     |

|                                  |                |               |               |
|----------------------------------|----------------|---------------|---------------|
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Lip injury                       |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Procedural pain                  |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Transfusion reaction             |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Wound                            |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Skin abrasion                    |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Stoma site haemorrhage           |                |               |               |
| subjects affected / exposed      | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 1              | 0             | 0             |
| Cardiac disorders                |                |               |               |
| Angina pectoris                  |                |               |               |
| subjects affected / exposed      | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 1              | 0             | 0             |
| Aortic valve incompetence        |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Arteriosclerosis coronary artery |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Atrioventricular block           |                |               |               |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0              | 0             | 0             |
| Bradycardia                      |                |               |               |
| subjects affected / exposed      | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 1              | 0             | 0             |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| Bundle branch block right   |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Cardiac arrest              |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Cardiac disorder            |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Cardiac failure             |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0             | 1              |
| Cardiac valve disease       |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Cardiomegaly                |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Cardiomyopathy              |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Cardiovascular disorder     |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Congestive cardiomyopathy   |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Extrasystoles               |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Heart valve incompetence    |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Hypertensive heart disease  |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0             | 1              |

|   |                     |                    |                     |
|---|---------------------|--------------------|---------------------|
| Left ventricular hypertrophy<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 8 (25.00%)<br>2 | 0 / 3 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Nervous system disorders<br>Burning sensation<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Dizziness   |                     |                    |                     |



|                               |                |                |                |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed   | 2 / 8 (25.00%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 3              | 1              | 0              |
| Headache                      |                |                |                |
| subjects affected / exposed   | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 1 / 6 (16.67%) |
| occurrences (all)             | 1              | 1              | 2              |
| Hemiparesis                   |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Orthostatic intolerance       |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Paraesthesia                  |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Peripheral sensory neuropathy |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Polyneuropathy                |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Sinus headache                |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Somnolence                    |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Syncope                       |                |                |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Tremor                        |                |                |                |
| subjects affected / exposed   | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)             | 2              | 0              | 1              |
| Ageusia                       |                |                |                |
| subjects affected / exposed   | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)             | 2              | 0              | 0              |
| Dysgeusia                     |                |                |                |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0              |
| Hypotonia                            |                |                |                |
| subjects affected / exposed          | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                    | 2              | 0              | 0              |
| Blood and lymphatic system disorders |                |                |                |
| Anaemia                              |                |                |                |
| subjects affected / exposed          | 3 / 8 (37.50%) | 1 / 3 (33.33%) | 4 / 6 (66.67%) |
| occurrences (all)                    | 6              | 1              | 6              |
| Febrile neutropenia                  |                |                |                |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Leukocytosis                         |                |                |                |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Leukopenia                           |                |                |                |
| subjects affected / exposed          | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 2 / 6 (33.33%) |
| occurrences (all)                    | 2              | 1              | 2              |
| Lymphadenopathy                      |                |                |                |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Neutropenia                          |                |                |                |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 3 / 6 (50.00%) |
| occurrences (all)                    | 0              | 0              | 5              |
| Splenomegaly                         |                |                |                |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0              |
| Thrombocytopenia                     |                |                |                |
| subjects affected / exposed          | 3 / 8 (37.50%) | 1 / 3 (33.33%) | 2 / 6 (33.33%) |
| occurrences (all)                    | 9              | 1              | 5              |
| Cytopenia                            |                |                |                |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 2 / 6 (33.33%) |
| occurrences (all)                    | 0              | 0              | 2              |
| Ear and labyrinth disorders          |                |                |                |
| Ear haemorrhage                      |                |                |                |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Vertigo                     |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Eye disorders               |               |                |                |
| Cataract                    |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Dry eye                     |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Erythema of eyelid          |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0             | 0              | 1              |
| Eye haemorrhage             |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Eyelid oedema               |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0             | 0              | 1              |
| Glaucoma                    |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Lacrimation increased       |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Macular degeneration        |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Visual acuity reduced       |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Visual impairment           |               |                |                |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0             | 0              | 1              |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| Hyphaema                    |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Photopsia                   |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Gastrointestinal disorders  |                |               |                |
| Abdominal pain              |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Abdominal pain upper        |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 1              | 0             | 1              |
| Abnormal faeces             |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Anal haemorrhage            |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Ascites                     |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Constipation                |                |               |                |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 3              | 0             | 1              |
| Diarrhoea                   |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 3 / 6 (50.00%) |
| occurrences (all)           | 1              | 0             | 5              |
| Dry mouth                   |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Dyspepsia                   |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Dysphagia                   |                |               |                |

|                               |                |               |                |
|-------------------------------|----------------|---------------|----------------|
| subjects affected / exposed   | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)             | 1              | 0             | 1              |
| Enterocolitis                 |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Faecaloma                     |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Flatulence                    |                |               |                |
| subjects affected / exposed   | 4 / 8 (50.00%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)             | 4              | 0             | 1              |
| Gastritis                     |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Gastrointestinal inflammation |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Gingival bleeding             |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)             | 0              | 0             | 3              |
| Gingival discolouration       |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Gingival pain                 |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Gingival swelling             |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)             | 0              | 0             | 1              |
| Glossodynia                   |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Haematochezia                 |                |               |                |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Haemorrhoids                  |                |               |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 1              | 0              | 1              |
| Hiatus hernia               |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Mouth haemorrhage           |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Mouth ulceration            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nausea                      |                |                |                |
| subjects affected / exposed | 4 / 8 (50.00%) | 2 / 3 (66.67%) | 1 / 6 (16.67%) |
| occurrences (all)           | 6              | 2              | 2              |
| Oesophagitis                |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Oral mucosal erythema       |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Oral pain                   |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Periodontal disease         |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Proctalgia                  |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rectal haemorrhage          |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Small intestine ulcer       |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Stomatitis                  |                |                |                |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Tongue coated               |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Tongue ulceration           |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Toothache                   |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Vomiting                    |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Anal incontinence           |                |                |               |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 2              | 0              | 0             |
| Aphthous ulcer              |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Tongue discolouration       |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Abdominal discomfort        |                |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Gastric ulcer               |                |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Gastrointestinal disorder   |                |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Palatal disorder            |                |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Tongue haemorrhage          |                |                |               |

|  |                     |                    |                    |
|--|---------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Hepatobiliary disorders                          |                     |                    |                    |
| Cholelithiasis                                   |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Hepatic congestion                               |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Hepatic cyst                                     |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Hepatic lesion                                   |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Hepatomegaly                                     |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Hyperbilirubinaemia                              |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Hepatic steatosis                                |                     |                    |                    |
| subjects affected / exposed                      | 1 / 8 (12.50%)      | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 1                   | 0                  | 0                  |
| Skin and subcutaneous tissue disorders           |                     |                    |                    |
| Alopecia   |                     |                    |                    |
| subjects affected / exposed                      | 2 / 8 (25.00%)      | 1 / 3 (33.33%)     | 3 / 6 (50.00%)     |
| occurrences (all)                                | 2                   | 1                  | 3                  |
| Blister  |                     |                    |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)       | 0 / 3 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Blood blister                                    |                     |                    |                    |
| subjects affected / exposed                      | 1 / 8 (12.50%)      | 0 / 3 (0.00%)      | 1 / 6 (16.67%)     |
| occurrences (all)                                | 1                   | 0                  | 1                  |
| Dermatitis atopic                                |                     |                    |                    |



|                                 |                |                |                |
|---------------------------------|----------------|----------------|----------------|
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Dermatitis exfoliative</b>   |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Dry skin</b>                 |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Erythema</b>                 |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Haemorrhage subcutaneous</b> |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)               | 0              | 0              | 1              |
| <b>Hyperhidrosis</b>            |                |                |                |
| subjects affected / exposed     | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)               | 1              | 1              | 0              |
| <b>Night sweats</b>             |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 3 / 6 (50.00%) |
| occurrences (all)               | 0              | 1              | 4              |
| <b>Pain of skin</b>             |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Parapsoriasis</b>            |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Petechiae</b>                |                |                |                |
| subjects affected / exposed     | 2 / 8 (25.00%) | 2 / 3 (66.67%) | 4 / 6 (66.67%) |
| occurrences (all)               | 2              | 2              | 4              |
| <b>Pruritus</b>                 |                |                |                |
| subjects affected / exposed     | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)               | 1              | 0              | 2              |
| <b>Psoriasis</b>                |                |                |                |
| subjects affected / exposed     | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| <b>Purpura</b>                  |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rash                        |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 3 / 6 (50.00%) |
| occurrences (all)           | 1              | 0              | 3              |
| Skin erosion                |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Skin haemorrhage            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Skin hyperpigmentation      |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Skin lesion                 |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Swelling face               |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Urticaria                   |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Eczema                      |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Ingrowing nail              |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Intertrigo                  |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Renal and urinary disorders |                |                |                |
| Anuria                      |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Bladder pain                |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Dysuria                     |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Glycosuria                  |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Haematuria                  |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Leukocyturia                |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Micturition disorder        |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nephropathy                 |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nocturia                    |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Pollakiuria                 |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Proteinuria                 |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Renal atrophy               |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Renal cyst                  |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |

|   |                     |                    |                    |
|---|---------------------|--------------------|--------------------|
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Renal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Urethral haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Urethral pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Incontinence<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Endocrine disorders<br>Adrenal disorder<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>3 | 0 / 3 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Arthritis   |                     |                    |                    |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Back pain                   |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0             | 1              |
| Bone lesion                 |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0             | 1              |
| Bone pain                   |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0             | 3              |
| Flank pain                  |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Groin pain                  |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Joint swelling              |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Muscle spasms               |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 1              | 0             | 2              |
| Muscular weakness           |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Musculoskeletal pain        |                |               |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Myalgia                     |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Myopathy                    |                |               |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Osteoarthritis              |                |               |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Osteolysis                              |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Osteopenia                              |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Osteoporosis                            |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Pain in extremity                       |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Spinal osteoarthritis                   |                |                |                |
| subjects affected / exposed             | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 1              | 0              | 0              |
| Infections and infestations             |                |                |                |
| Bacterial infection                     |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Beta haemolytic streptococcal infection |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 1              | 0              |
| Bronchitis                              |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 1              | 0              |
| Candida infection                       |                |                |                |
| subjects affected / exposed             | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 1              | 0              | 0              |
| Clostridium difficile infection         |                |                |                |
| subjects affected / exposed             | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Cystitis                                |                |                |                |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Device related infection    |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Diverticulitis              |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Enterococcal infection      |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Erysipelas                  |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Escherichia bacteraemia     |                |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Escherichia infection       |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Fungal infection            |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Fungal skin infection       |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Fusobacterium infection     |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Gingivitis                  |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Herpes simplex              |                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Herpes virus infection      |                |                |               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Herpes zoster               |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Micrococcus infection       |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Nail bed infection          |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nasopharyngitis             |                |                |                |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0              |
| Oral candidiasis            |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Oral herpes                 |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Pharyngitis                 |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Pneumonia                   |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Pneumonia fungal            |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Pseudomonas infection       |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Sepsis                      |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Skin infection              |                |                |                |



|                                    |                |                |                |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |
| Staphylococcal infection           |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 1 / 3 (33.33%) | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 1              | 0              |
| Urinary tract infection            |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |
| Urosepsis                          |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |
| Osteomyelitis                      |                |                |                |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0              |
| Post procedural infection          |                |                |                |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0              |
| Soft tissue infection              |                |                |                |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0              |
| Metabolism and nutrition disorders |                |                |                |
| Acidosis                           |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |
| Alkalosis                          |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |
| Decreased appetite                 |                |                |                |
| subjects affected / exposed        | 2 / 8 (25.00%) | 1 / 3 (33.33%) | 2 / 6 (33.33%) |
| occurrences (all)                  | 5              | 1              | 2              |
| Dehydration                        |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |
| Diabetes mellitus                  |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0              |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Hypercalcaemia              |                |                 |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Hypercholesterolaemia       |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hyperglycaemia              |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hyperkalaemia               |                |                 |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Hypernatraemia              |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hyperuricaemia              |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypoalbuminaemia            |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypocalcaemia               |                |                 |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%)   | 1 / 6 (16.67%) |
| occurrences (all)           | 1              | 0               | 1              |
| Hypoglycaemia               |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypokalaemia                |                |                 |                |
| subjects affected / exposed | 6 / 8 (75.00%) | 3 / 3 (100.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 6              | 3               | 0              |
| Hyponatraemia               |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypoproteinaemia            |                |                 |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%)   | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |

|                             |                |               |               |
|-----------------------------|----------------|---------------|---------------|
| Iron overload               |                |               |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Uraemic acidosis            |                |               |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Vitamin D deficiency        |                |               |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Fluid overload              |                |               |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 3 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 1              | 0             | 0             |

| <b>Non-serious adverse events</b>                                   | Phase I Schedule B.<br>Volasertib 350 mg | Phase I Schedule B.<br>Volasertib 150 mg | Phase I Schedule B.<br>Volasertib 200 mg |
|---|--|--|--|
| Total subjects affected by non-serious adverse events               |  |  |  |
| subjects affected / exposed   | 5 / 5 (100.00%)                          | 11 / 11 (100.00%)                        | 2 / 2 (100.00%)                          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Chloroma  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 11 (0.00%)                           | 0 / 2 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Leukaemia cutis   |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 1 / 11 (9.09%)                           | 0 / 2 (0.00%)                            |
| occurrences (all)   | 0  | 1  | 0  |
| Meningioma  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 11 (0.00%)                           | 0 / 2 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Neoplasm progression  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 11 (0.00%)                           | 0 / 2 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Small intestine carcinoma   |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 11 (0.00%)                           | 0 / 2 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Vascular disorders  |  |  |  |
| Angiopathy  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 11 (0.00%)                           | 0 / 2 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |

|                             |               |                 |                |
|-----------------------------|---------------|-----------------|----------------|
| Circulatory collapse        |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Haematoma                   |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 11 (18.18%) | 1 / 2 (50.00%) |
| occurrences (all)           | 0             | 2               | 1              |
| Haemorrhage                 |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Hypertension                |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Hypertensive crisis         |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Hypotension                 |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Infarction                  |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Peripheral coldness         |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Peripheral embolism         |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Thrombophlebitis            |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Varicose vein               |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Lymphoedema                 |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |

|  |                     |                     |                    |
|--|---------------------|---------------------|--------------------|
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Surgical and medical procedures  |                     |                     |                    |
| Central venous catheterisation<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Nail operation<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| General disorders and administration<br>site conditions                            |                     |                     |                    |
| Adverse drug reaction<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1 | 0 / 2 (0.00%)<br>0 |
| Calcinosis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Catheter site erythema<br>subjects affected / exposed<br>occurrences (all)         | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Catheter site oedema<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)               | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 5 (20.00%)<br>1 | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Chills<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 5 (20.00%)<br>1 | 1 / 11 (9.09%)<br>1 | 0 / 2 (0.00%)<br>0 |
| Fatigue  |                     |                     |                    |

|                                       |                |                 |                 |
|---------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed           | 1 / 5 (20.00%) | 3 / 11 (27.27%) | 2 / 2 (100.00%) |
| occurrences (all)                     | 1              | 3               | 2               |
| Feeling cold                          |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Feeling hot                           |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Feeling of body temperature change    |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Gait disturbance                      |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| General physical health deterioration |                |                 |                 |
| subjects affected / exposed           | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 1              | 1               | 0               |
| Granuloma                             |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Induration                            |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Inflammation                          |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Influenza like illness                |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Infusion site pain                    |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Injection site haematoma              |                |                 |                 |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                     | 0              | 0               | 0               |
| Injection site reaction               |                |                 |                 |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Local swelling              |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Localised oedema            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Malaise                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mucosal inflammation        |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 1              | 1               | 0              |
| Oedema                      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Oedema mucosal              |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oedema peripheral           |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 11 (18.18%) | 1 / 2 (50.00%) |
| occurrences (all)           | 1              | 2               | 1              |
| Pain                        |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 3 / 11 (27.27%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 1              | 3               | 0              |
| Puncture site pain          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pyrexia                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 3               | 0              |
| Thirst decreased            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Peripheral swelling         |                |                 |                |

|  |               |                |               |
|--|---------------|----------------|---------------|
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Catheter site pain                       |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Hyperthermia                             |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Discomfort                               |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Mucosal haemorrhage                      |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Social circumstances                     |               |                |               |
| Fasting                                  |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Reproductive system and breast disorders |               |                |               |
| Breast enlargement                       |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Genital swelling                         |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Haematospermia                           |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 1              | 0             |
| Nipple disorder                          |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Pelvic pain                              |               |                |               |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                        | 0             | 0              | 0             |
| Penile oedema                            |               |                |               |



|   |                |                 |               |
|---|----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Scrotal oedema                                  |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Vaginal haemorrhage                             |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Vulvovaginal erythema                           |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Genital burning sensation                       |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Respiratory, thoracic and mediastinal disorders |                |                 |               |
| Atelectasis                                     |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Bronchial secretion retention                   |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Dysphonia                                       |                |                 |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 1              | 1               | 0             |
| Cough   |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 2               | 0             |
| Dyspnoea  |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0             |
| Dyspnoea exertional                             |                |                 |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 1              | 1               | 0             |
| Haemoptysis                                     |                |                 |               |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Epistaxis                   |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 11 (18.18%) | 1 / 2 (50.00%) |
| occurrences (all)           | 2              | 2               | 2              |
| Hiccups                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Laryngeal disorder          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Lung infiltration           |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Lung disorder               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Nasal inflammation          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oropharyngeal pain          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pharyngeal inflammation     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pleural effusion            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Productive cough            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pulmonary hypertension      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Respiratory failure         |                |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Sputum discoloured          |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Sputum retention            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Vocal cord disorder         |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rales                       |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rhonchi                     |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Throat irritation           |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Psychiatric disorders       |                |                |                |
| Agitation                   |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Anxiety                     |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Communication disorder      |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Confusional state           |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Depressed mood              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |

|   |                |                 |               |
|---|----------------|-----------------|---------------|
| Depression                                      |                |                 |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0             |
| Disorientation                                  |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Hallucination                                   |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Hallucination, visual                           |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Initial insomnia                                |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Insomnia  |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Panic attack                                    |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Restlessness                                    |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Sleep disorder                                  |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 2               | 0             |
| Suicidal ideation                               |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Investigations                                  |                |                 |               |
| Activated partial thromboplastin time prolonged |                |                 |               |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                               | 0              | 2               | 0             |
| Activated partial thromboplastin time shortened |                |                 |               |

|  |               |                 |                |
|--|---------------|-----------------|----------------|
| subjects affected / exposed            | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 1               | 0              |
| Alanine aminotransferase increased     |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 2 / 11 (18.18%) | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 2               | 0              |
| Aspartate aminotransferase increased   |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 1 / 2 (50.00%) |
| occurrences (all)                      | 0             | 1               | 1              |
| Blast cell count increased             |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 1               | 0              |
| Blood albumin decreased                |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 0               | 0              |
| Blood albumin increased                |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 0               | 0              |
| Blood alkaline phosphatase increased   |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 3 / 11 (27.27%) | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 6               | 0              |
| Blood bilirubin increased              |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 2 / 11 (18.18%) | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 2               | 0              |
| Blood chloride increased               |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 1               | 0              |
| Blood creatine phosphokinase decreased |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 0               | 0              |
| Blood creatine phosphokinase increased |               |                 |                |
| subjects affected / exposed            | 0 / 5 (0.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0             | 0               | 0              |
| Blood creatinine                       |               |                 |                |

|                                       |                |                 |                |
|---------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 0               | 0              |
| Blood creatinine decreased            |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 0               | 0              |
| Blood creatinine increased            |                |                 |                |
| subjects affected / exposed           | 2 / 5 (40.00%) | 2 / 11 (18.18%) | 1 / 2 (50.00%) |
| occurrences (all)                     | 2              | 3               | 1              |
| Blood fibrinogen increased            |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 1               | 0              |
| Blood glucose increased               |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 1               | 0              |
| Blood iron decreased                  |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 0               | 0              |
| Blood iron increased                  |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 0               | 0              |
| Blood lactate dehydrogenase decreased |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 1               | 0              |
| Blood lactate dehydrogenase increased |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 4 / 11 (36.36%) | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 4               | 0              |
| Blood phosphorus decreased            |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 1               | 0              |
| Blood potassium decreased             |                |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                     | 0              | 0               | 0              |
| Blood pressure increased              |                |                 |                |

|                                |                |                 |                 |
|--------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed    | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 1               | 0               |
| Blood triglycerides increased  |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| Blood urea decreased           |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| Blood urea increased           |                |                 |                 |
| subjects affected / exposed    | 1 / 5 (20.00%) | 3 / 11 (27.27%) | 1 / 2 (50.00%)  |
| occurrences (all)              | 1              | 3               | 1               |
| Blood uric acid increased      |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 1 / 2 (50.00%)  |
| occurrences (all)              | 0              | 1               | 1               |
| Blood urine present            |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| Body temperature increased     |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 2               | 0               |
| Breath sounds abnormal         |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| C-reactive protein increased   |                |                 |                 |
| subjects affected / exposed    | 1 / 5 (20.00%) | 4 / 11 (36.36%) | 2 / 2 (100.00%) |
| occurrences (all)              | 1              | 4               | 2               |
| Candida test positive          |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| Ejection fraction decreased    |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| Electrocardiogram QT prolonged |                |                 |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)              | 0              | 0               | 0               |
| Electrocardiogram change       |                |                 |                 |

|                                      |                |                 |               |
|--------------------------------------|----------------|-----------------|---------------|
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Enterococcus test positive           |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Escherichia test positive            |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Gamma-glutamyltransferase increased  |                |                 |               |
| subjects affected / exposed          | 1 / 5 (20.00%) | 4 / 11 (36.36%) | 0 / 2 (0.00%) |
| occurrences (all)                    | 1              | 4               | 0             |
| Heart rate increased                 |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Hepatic enzyme increased             |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Liver function test abnormal         |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Oxygen saturation decreased          |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Prostatic specific antigen increased |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0             |
| Protein total decreased              |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 3 / 11 (27.27%) | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 3               | 0             |
| Prothrombin time prolonged           |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Serum ferritin increased             |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0             |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Thrombin time shortened<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Troponin increased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 5 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1 | 0 / 2 (0.00%)<br>0  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 5 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1 | 1 / 2 (50.00%)<br>1 |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| International normalised ratio increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Allergic transfusion reaction<br>subjects affected / exposed<br>occurrences (all)            | 2 / 5 (40.00%)<br>2 | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Drug administration error<br>subjects affected / exposed<br>occurrences (all)                | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 1 / 2 (50.00%)<br>1 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Laceration   |                     |                     |                     |

|                                  |               |                |               |
|----------------------------------|---------------|----------------|---------------|
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Lip injury                       |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 1              | 0             |
| Procedural pain                  |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Transfusion reaction             |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Wound                            |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Skin abrasion                    |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Stoma site haemorrhage           |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Cardiac disorders                |               |                |               |
| Angina pectoris                  |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Aortic valve incompetence        |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |
| Arteriosclerosis coronary artery |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 1              | 0             |
| Atrioventricular block           |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 1              | 0             |
| Bradycardia                      |               |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                | 0             | 0              | 0             |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| Bundle branch block right   |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Cardiac arrest              |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiac disorder            |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiac failure             |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Cardiac valve disease       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiomegaly                |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Cardiomyopathy              |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiovascular disorder     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Congestive cardiomyopathy   |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Extrasystoles               |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Heart valve incompetence    |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Hypertensive heart disease  |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |

|   |                    |                      |                    |
|---|--------------------|----------------------|--------------------|
| Left ventricular hypertrophy<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0 | 2 / 11 (18.18%)<br>2 | 0 / 2 (0.00%)<br>0 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0 | 2 / 11 (18.18%)<br>2 | 0 / 2 (0.00%)<br>0 |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Nervous system disorders<br>Burning sensation<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 |
| Dizziness   |                    |                      |                    |

|                               |                |                |               |
|-------------------------------|----------------|----------------|---------------|
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 1              | 0             |
| Headache                      |                |                |               |
| subjects affected / exposed   | 2 / 5 (40.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)             | 3              | 1              | 0             |
| Hemiparesis                   |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Orthostatic intolerance       |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Paraesthesia                  |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 1              | 0             |
| Peripheral sensory neuropathy |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Polyneuropathy                |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Sinus headache                |                |                |               |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 1              | 0              | 0             |
| Somnolence                    |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Syncope                       |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Tremor                        |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Ageusia                       |                |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0              | 0              | 0             |
| Dysgeusia                     |                |                |               |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                        | 0 / 5 (0.00%)<br>0   | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0   |
| Hypotonia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0   | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0   |
| Blood and lymphatic system disorders                                    |                      |                      |                      |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)             | 5 / 5 (100.00%)<br>6 | 4 / 11 (36.36%)<br>4 | 2 / 2 (100.00%)<br>2 |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1  | 1 / 11 (9.09%)<br>1  | 0 / 2 (0.00%)<br>0   |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 5 (0.00%)<br>0   | 4 / 11 (36.36%)<br>5 | 0 / 2 (0.00%)<br>0   |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 5 (20.00%)<br>2  | 2 / 11 (18.18%)<br>3 | 1 / 2 (50.00%)<br>1  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)     | 0 / 5 (0.00%)<br>0   | 1 / 11 (9.09%)<br>1  | 1 / 2 (50.00%)<br>1  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 5 (20.00%)<br>1  | 2 / 11 (18.18%)<br>3 | 1 / 2 (50.00%)<br>1  |
| Splenomegaly<br>subjects affected / exposed<br>occurrences (all)        | 0 / 5 (0.00%)<br>0   | 1 / 11 (9.09%)<br>1  | 1 / 2 (50.00%)<br>1  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)    | 3 / 5 (60.00%)<br>3  | 5 / 11 (45.45%)<br>5 | 1 / 2 (50.00%)<br>1  |
| Cytopenia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0   | 0 / 11 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0   |
| Ear and labyrinth disorders   |                      |                      |                      |
| Ear haemorrhage   |                      |                      |                      |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Vertigo                     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Eye disorders               |                |                |               |
| Cataract                    |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Dry eye                     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Erythema of eyelid          |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Eye haemorrhage             |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Eyelid oedema               |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Glaucoma                    |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Lacrimation increased       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Macular degeneration        |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Visual acuity reduced       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Visual impairment           |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 2              | 0              | 0             |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Hyphaema                    |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Photopsia                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gastrointestinal disorders  |                |                 |                |
| Abdominal pain              |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Abdominal pain upper        |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Abnormal faeces             |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Anal haemorrhage            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Ascites                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Constipation                |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 11 (27.27%) | 1 / 2 (50.00%) |
| occurrences (all)           | 0              | 4               | 1              |
| Diarrhoea                   |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 3              | 1               | 0              |
| Dry mouth                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dyspepsia                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dysphagia                   |                |                 |                |



|                               |               |                |               |
|-------------------------------|---------------|----------------|---------------|
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Enterocolitis                 |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Faecaloma                     |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Flatulence                    |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Gastritis                     |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Gastrointestinal inflammation |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Gingival bleeding             |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Gingival discolouration       |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Gingival pain                 |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Gingival swelling             |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Glossodynia                   |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Haematochezia                 |               |                |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)             | 0             | 0              | 0             |
| Haemorrhoids                  |               |                |               |

|                             |                |                 |               |
|-----------------------------|----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Hiatus hernia               |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Mouth haemorrhage           |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Mouth ulceration            |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Nausea                      |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 2               | 0             |
| Oesophagitis                |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Oral mucosal erythema       |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Oral pain                   |                |                 |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 0               | 0             |
| Periodontal disease         |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1               | 0             |
| Proctalgia                  |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1               | 0             |
| Rectal haemorrhage          |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Small intestine ulcer       |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Stomatitis                  |                |                 |               |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Tongue coated               |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tongue ulceration           |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Toothache                   |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Vomiting                    |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 1 / 2 (50.00%) |
| occurrences (all)           | 0             | 1              | 1              |
| Anal incontinence           |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Aphthous ulcer              |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tongue discolouration       |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Abdominal discomfort        |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gastric ulcer               |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gastrointestinal disorder   |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Palatal disorder            |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tongue haemorrhage          |               |                |                |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 |
| Hepatobiliary disorders                          |                    |                     |                    |
| Cholelithiasis                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic congestion                               |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 1 / 11 (9.09%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |
| Hepatic cyst                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic lesion                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatomegaly                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 1 / 11 (9.09%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |
| Hyperbilirubinaemia                              |                    |                     |                    |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Hepatic steatosis                                |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Skin and subcutaneous tissue disorders           |                    |                     |                    |
| Alopecia   |                    |                     |                    |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Blister  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 11 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Blood blister                                    |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 1 / 11 (9.09%)      | 2 / 2 (100.00%)    |
| occurrences (all)                                | 0                  | 1                   | 2                  |
| Dermatitis atopic                                |                    |                     |                    |

|                                 |                |                 |                |
|---------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Dermatitis exfoliative</b>   |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Dry skin</b>                 |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Erythema</b>                 |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Haemorrhage subcutaneous</b> |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 1 / 2 (50.00%) |
| occurrences (all)               | 0              | 0               | 1              |
| <b>Hyperhidrosis</b>            |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 2               | 0              |
| <b>Night sweats</b>             |                |                 |                |
| subjects affected / exposed     | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 1              | 1               | 0              |
| <b>Pain of skin</b>             |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Parapsoriasis</b>            |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Petechiae</b>                |                |                 |                |
| subjects affected / exposed     | 1 / 5 (20.00%) | 4 / 11 (36.36%) | 0 / 2 (0.00%)  |
| occurrences (all)               | 1              | 4               | 0              |
| <b>Pruritus</b>                 |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Psoriasis</b>                |                |                 |                |
| subjects affected / exposed     | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)               | 0              | 0               | 0              |
| <b>Purpura</b>                  |                |                 |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Rash                        |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 11 (18.18%) | 1 / 2 (50.00%) |
| occurrences (all)           | 1              | 2               | 1              |
| Skin erosion                |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Skin haemorrhage            |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Skin hyperpigmentation      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Skin lesion                 |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Swelling face               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Urticaria                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Eczema                      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Ingrowing nail              |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Intertrigo                  |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Renal and urinary disorders |                |                 |                |
| Anuria                      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 1 / 2 (50.00%) |
| occurrences (all)           | 0              | 0               | 1              |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Bladder pain                |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Dysuria                     |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Glycosuria                  |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Haematuria                  |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Leukocyturia                |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Micturition disorder        |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Nephropathy                 |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Nocturia                    |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Pollakiuria                 |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Proteinuria                 |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Renal atrophy               |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Renal cyst                  |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Renal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Urethral haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 1 / 2 (50.00%)<br>1 |
| Urethral pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Endocrine disorders<br>Adrenal disorder<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 11 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  |
| Arthritis   |                     |                     |                     |



|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Back pain                   |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Bone lesion                 |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Bone pain                   |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Flank pain                  |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Groin pain                  |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Joint swelling              |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Muscle spasms               |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Muscular weakness           |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Musculoskeletal pain        |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Myalgia                     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Myopathy                    |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Osteoarthritis              |                |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Osteolysis                              |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Osteopenia                              |                |                |               |
| subjects affected / exposed             | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0             |
| Osteoporosis                            |                |                |               |
| subjects affected / exposed             | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0             |
| Pain in extremity                       |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0             |
| Spinal osteoarthritis                   |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0             |
| Infections and infestations             |                |                |               |
| Bacterial infection                     |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Beta haemolytic streptococcal infection |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Bronchitis                              |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Candida infection                       |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Clostridium difficile infection         |                |                |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)                       | 0              | 0              | 0             |
| Cystitis                                |                |                |               |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all)           | 0             | 0              | 1              |
| Device related infection    |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Diverticulitis              |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Enterococcal infection      |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Erysipelas                  |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Escherichia bacteraemia     |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Escherichia infection       |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Fungal infection            |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Fungal skin infection       |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Fusobacterium infection     |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gingivitis                  |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Herpes simplex              |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Herpes virus infection      |               |                |                |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Herpes zoster               |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Micrococcus infection       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Nail bed infection          |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Nasopharyngitis             |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 1              | 0             |
| Oral candidiasis            |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Oral herpes                 |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Pharyngitis                 |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Pneumonia                   |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Pneumonia fungal            |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Pseudomonas infection       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Sepsis                      |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Skin infection              |                |                |               |

|                                    |                |                 |               |
|------------------------------------|----------------|-----------------|---------------|
| subjects affected / exposed        | 1 / 5 (20.00%) | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0             |
| Staphylococcal infection           |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Urinary tract infection            |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Urosepsis                          |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Osteomyelitis                      |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Post procedural infection          |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Soft tissue infection              |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Metabolism and nutrition disorders |                |                 |               |
| Acidosis                           |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Alkalosis                          |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |
| Decreased appetite                 |                |                 |               |
| subjects affected / exposed        | 1 / 5 (20.00%) | 3 / 11 (27.27%) | 0 / 2 (0.00%) |
| occurrences (all)                  | 1              | 3               | 0             |
| Dehydration                        |                |                 |               |
| subjects affected / exposed        | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 1              | 1               | 0             |
| Diabetes mellitus                  |                |                 |               |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0             |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Hypercalcaemia              |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0               |
| Hypercholesterolaemia       |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0               |
| Hyperglycaemia              |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 2 / 2 (100.00%) |
| occurrences (all)           | 0              | 2               | 2               |
| Hyperkalaemia               |                |                 |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 1              | 1               | 0               |
| Hypernatraemia              |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0               |
| Hyperuricaemia              |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 3               | 0               |
| Hypoalbuminaemia            |                |                 |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 11 (9.09%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 1              | 1               | 0               |
| Hypocalcaemia               |                |                 |                 |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 11 (18.18%) | 2 / 2 (100.00%) |
| occurrences (all)           | 2              | 2               | 2               |
| Hypoglycaemia               |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0               |
| Hypokalaemia                |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 11 (18.18%) | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 3               | 0               |
| Hyponatraemia               |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%)  | 1 / 2 (50.00%)  |
| occurrences (all)           | 0              | 1               | 1               |
| Hypoproteinaemia            |                |                 |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)           | 0              | 0               | 0               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Iron overload               |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Uraemic acidosis            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Vitamin D deficiency        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 11 (9.09%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Fluid overload              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 11 (0.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |

| <b>Non-serious adverse events</b>                                   | Phase I Schedule B.<br>Volasertib 500 mg | Phase I Schedule B.<br>Volasertib 450 mg | Phase I Schedule B.<br>Volasertib 550 mg |
|---|--|--|--|
| Total subjects affected by non-serious adverse events               |  |  |  |
| subjects affected / exposed   | 5 / 5 (100.00%)                          | 23 / 23 (100.00%)                        | 4 / 4 (100.00%)                          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Chloroma  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 1 / 23 (4.35%)                           | 0 / 4 (0.00%)                            |
| occurrences (all)   | 0  | 1  | 0  |
| Leukaemia cutis   |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Meningioma  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Neoplasm progression  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Small intestine carcinoma   |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |
| Vascular disorders  |  |  |  |
| Angiopathy  |  |  |  |
| subjects affected / exposed   | 0 / 5 (0.00%)                            | 0 / 23 (0.00%)                           | 0 / 4 (0.00%)                            |
| occurrences (all)   | 0  | 0  | 0  |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Circulatory collapse        |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Haematoma                   |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 2              | 3               | 0              |
| Haemorrhage                 |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypertension                |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 5 / 23 (21.74%) | 2 / 4 (50.00%) |
| occurrences (all)           | 1              | 5               | 3              |
| Hypertensive crisis         |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypotension                 |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Infarction                  |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Peripheral coldness         |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Peripheral embolism         |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Thrombophlebitis            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Varicose vein               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Lymphoedema                 |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |



|  |                     |                     |                    |
|--|---------------------|---------------------|--------------------|
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Surgical and medical procedures  |                     |                     |                    |
| Central venous catheterisation<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Nail operation<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| General disorders and administration<br>site conditions                            |                     |                     |                    |
| Adverse drug reaction<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Calcinosis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Catheter site erythema<br>subjects affected / exposed<br>occurrences (all)         | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Catheter site oedema<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)               | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Chills<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 5 (40.00%)<br>2 | 1 / 23 (4.35%)<br>1 | 0 / 4 (0.00%)<br>0 |
| Fatigue  |                     |                     |                    |

|                                       |                |                  |                |
|---------------------------------------|----------------|------------------|----------------|
| subjects affected / exposed           | 2 / 5 (40.00%) | 4 / 23 (17.39%)  | 2 / 4 (50.00%) |
| occurrences (all)                     | 2              | 5                | 2              |
| Feeling cold                          |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 1 / 4 (25.00%) |
| occurrences (all)                     | 0              | 0                | 1              |
| Feeling hot                           |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Feeling of body temperature change    |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 1 / 4 (25.00%) |
| occurrences (all)                     | 0              | 0                | 1              |
| Gait disturbance                      |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| General physical health deterioration |                |                  |                |
| subjects affected / exposed           | 1 / 5 (20.00%) | 13 / 23 (56.52%) | 0 / 4 (0.00%)  |
| occurrences (all)                     | 1              | 13               | 0              |
| Granuloma                             |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Induration                            |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Inflammation                          |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 2 / 23 (8.70%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 2                | 0              |
| Influenza like illness                |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 1                | 0              |
| Infusion site pain                    |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Injection site haematoma              |                |                  |                |
| subjects affected / exposed           | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0              | 0                | 0              |
| Injection site reaction               |                |                  |                |

|                             |               |                 |                |
|-----------------------------|---------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Local swelling              |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Localised oedema            |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Malaise                     |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Mucosal inflammation        |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 23 (8.70%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 2               | 0              |
| Oedema                      |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 23 (13.04%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0             | 4               | 1              |
| Oedema mucosal              |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Oedema peripheral           |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 9 / 23 (39.13%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 9               | 0              |
| Pain                        |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 3               | 0              |
| Puncture site pain          |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Pyrexia                     |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 23 (8.70%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 2               | 0              |
| Thirst decreased            |               |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Peripheral swelling         |               |                 |                |

|  |               |                |                |
|--|---------------|----------------|----------------|
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Catheter site pain                       |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Hyperthermia                             |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Discomfort                               |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Mucosal haemorrhage                      |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Social circumstances                     |               |                |                |
| Fasting                                  |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Reproductive system and breast disorders |               |                |                |
| Breast enlargement                       |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Genital swelling                         |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Haematospermia                           |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Nipple disorder                          |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                        | 0             | 0              | 0              |
| Pelvic pain                              |               |                |                |
| subjects affected / exposed              | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all)                        | 0             | 0              | 1              |
| Penile oedema                            |               |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Scrotal oedema                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Vaginal haemorrhage                             |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 1 / 4 (25.00%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Vulvovaginal erythema                           |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Genital burning sensation                       |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                 |                |
| Atelectasis                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Bronchial secretion retention                   |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Dysphonia                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0              |
| Cough   |                |                 |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 6 / 23 (26.09%) | 0 / 4 (0.00%)  |
| occurrences (all)                               | 1              | 10              | 0              |
| Dyspnoea  |                |                 |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 4 / 23 (17.39%) | 0 / 4 (0.00%)  |
| occurrences (all)                               | 1              | 4               | 0              |
| Dyspnoea exertional                             |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0              |
| Haemoptysis                                     |                |                 |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 1               | 1              |
| Epistaxis                   |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 5 / 23 (21.74%) | 1 / 4 (25.00%) |
| occurrences (all)           | 2              | 6               | 1              |
| Hiccups                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Laryngeal disorder          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Lung infiltration           |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Lung disorder               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Nasal inflammation          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oropharyngeal pain          |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 3               | 0              |
| Pharyngeal inflammation     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Pleural effusion            |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 23 (8.70%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 2               | 0              |
| Productive cough            |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Pulmonary hypertension      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Respiratory failure         |                |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Sputum discoloured          |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Sputum retention            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Vocal cord disorder         |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rales                       |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rhonchi                     |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Throat irritation           |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Psychiatric disorders       |                |                |                |
| Agitation                   |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Anxiety                     |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0              |
| Communication disorder      |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Confusional state           |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 2              | 1              |
| Depressed mood              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| Depression                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0              |
| Disorientation                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Hallucination                                   |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 1 / 4 (25.00%) |
| occurrences (all)                               | 0              | 1               | 1              |
| Hallucination, visual                           |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 1 / 4 (25.00%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Initial insomnia                                |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Insomnia  |                |                 |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 1              | 0               | 0              |
| Panic attack                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Restlessness                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 1 / 4 (25.00%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Sleep disorder                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 1 / 4 (25.00%) |
| occurrences (all)                               | 0              | 1               | 1              |
| Suicidal ideation                               |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Investigations                                  |                |                 |                |
| Activated partial thromboplastin time prolonged |                |                 |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 1 / 4 (25.00%) |
| occurrences (all)                               | 0              | 5               | 1              |
| Activated partial thromboplastin time shortened |                |                 |                |



|  |                |                 |               |
|--|----------------|-----------------|---------------|
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Alanine aminotransferase increased     |                |                 |               |
| subjects affected / exposed            | 1 / 5 (20.00%) | 4 / 23 (17.39%) | 0 / 4 (0.00%) |
| occurrences (all)                      | 1              | 4               | 0             |
| Aspartate aminotransferase increased   |                |                 |               |
| subjects affected / exposed            | 1 / 5 (20.00%) | 5 / 23 (21.74%) | 0 / 4 (0.00%) |
| occurrences (all)                      | 1              | 7               | 0             |
| Blast cell count increased             |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Blood albumin decreased                |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Blood albumin increased                |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Blood alkaline phosphatase increased   |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 3               | 0             |
| Blood bilirubin increased              |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 7               | 0             |
| Blood chloride increased               |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Blood creatine phosphokinase decreased |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Blood creatine phosphokinase increased |                |                 |               |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                      | 0              | 0               | 0             |
| Blood creatinine                       |                |                 |               |

|                                       |               |                 |                |
|---------------------------------------|---------------|-----------------|----------------|
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood creatinine decreased            |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood creatinine increased            |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 6 / 23 (26.09%) | 2 / 4 (50.00%) |
| occurrences (all)                     | 0             | 12              | 2              |
| Blood fibrinogen increased            |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood glucose increased               |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 4               | 0              |
| Blood iron decreased                  |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood iron increased                  |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood lactate dehydrogenase decreased |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood lactate dehydrogenase increased |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 5               | 0              |
| Blood phosphorus decreased            |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 0               | 0              |
| Blood potassium decreased             |               |                 |                |
| subjects affected / exposed           | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                     | 0             | 1               | 0              |
| Blood pressure increased              |               |                 |                |

|                                |                |                 |                |
|--------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood triglycerides increased  |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood urea decreased           |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood urea increased           |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Blood uric acid increased      |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 1 / 4 (25.00%) |
| occurrences (all)              | 0              | 4               | 2              |
| Blood urine present            |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Body temperature increased     |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 1               | 0              |
| Breath sounds abnormal         |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| C-reactive protein increased   |                |                 |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 7 / 23 (30.43%) | 3 / 4 (75.00%) |
| occurrences (all)              | 1              | 8               | 3              |
| Candida test positive          |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Ejection fraction decreased    |                |                 |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0               | 0              |
| Electrocardiogram QT prolonged |                |                 |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 5 / 23 (21.74%) | 1 / 4 (25.00%) |
| occurrences (all)              | 1              | 14              | 1              |
| Electrocardiogram change       |                |                 |                |

|                                      |                |                 |               |
|--------------------------------------|----------------|-----------------|---------------|
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Enterococcus test positive           |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Escherichia test positive            |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Gamma-glutamyltransferase increased  |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 3               | 0             |
| Heart rate increased                 |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Hepatic enzyme increased             |                |                 |               |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 1              | 0               | 0             |
| Liver function test abnormal         |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Oxygen saturation decreased          |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Prostatic specific antigen increased |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |
| Protein total decreased              |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 2               | 0             |
| Prothrombin time prolonged           |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 3               | 0             |
| Serum ferritin increased             |                |                 |               |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0             |

|   |                     |                      |                     |
|---|---------------------|----------------------|---------------------|
| Thrombin time shortened<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 5 (20.00%)<br>1 | 3 / 23 (13.04%)<br>5 | 0 / 4 (0.00%)<br>0  |
| Troponin increased<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| International normalised ratio<br>increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Injury, poisoning and procedural<br>complications   |                     |                      |                     |
| Allergic transfusion reaction<br>subjects affected / exposed<br>occurrences (all)               | 0 / 5 (0.00%)<br>0  | 1 / 23 (4.35%)<br>1  | 0 / 4 (0.00%)<br>0  |
| Drug administration error<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Fall<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1 | 4 / 23 (17.39%)<br>4 | 0 / 4 (0.00%)<br>0  |
| Laceration  |                     |                      |                     |

|                                  |                |                |               |
|----------------------------------|----------------|----------------|---------------|
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Lip injury                       |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Procedural pain                  |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Transfusion reaction             |                |                |               |
| subjects affected / exposed      | 1 / 5 (20.00%) | 2 / 23 (8.70%) | 0 / 4 (0.00%) |
| occurrences (all)                | 1              | 2              | 0             |
| Wound                            |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Skin abrasion                    |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 1              | 0             |
| Stoma site haemorrhage           |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Cardiac disorders                |                |                |               |
| Angina pectoris                  |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Aortic valve incompetence        |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Arteriosclerosis coronary artery |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Atrioventricular block           |                |                |               |
| subjects affected / exposed      | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                | 0              | 0              | 0             |
| Bradycardia                      |                |                |               |
| subjects affected / exposed      | 1 / 5 (20.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)                | 1              | 2              | 0             |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| Bundle branch block right   |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 2              | 0             |
| Cardiac arrest              |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Cardiac disorder            |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiac failure             |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiac valve disease       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiomegaly                |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiomyopathy              |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Cardiovascular disorder     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Congestive cardiomyopathy   |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Extrasystoles               |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Heart valve incompetence    |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Hypertensive heart disease  |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |

|   |                    |                     |                    |
|---|--------------------|---------------------|--------------------|
| Left ventricular hypertrophy<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 5 (0.00%)<br>0 | 1 / 23 (4.35%)<br>1 | 0 / 4 (0.00%)<br>0 |
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Nervous system disorders<br>Burning sensation<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Dizziness   |                    |                     |                    |



|                               |                |                 |                |
|-------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed   | 0 / 5 (0.00%)  | 4 / 23 (17.39%) | 1 / 4 (25.00%) |
| occurrences (all)             | 0              | 4               | 1              |
| Headache                      |                |                 |                |
| subjects affected / exposed   | 2 / 5 (40.00%) | 5 / 23 (21.74%) | 1 / 4 (25.00%) |
| occurrences (all)             | 3              | 6               | 1              |
| Hemiparesis                   |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0              |
| Orthostatic intolerance       |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Paraesthesia                  |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Peripheral sensory neuropathy |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Polyneuropathy                |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Sinus headache                |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Somnolence                    |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Syncope                       |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 1 / 4 (25.00%) |
| occurrences (all)             | 0              | 1               | 1              |
| Tremor                        |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 1 / 4 (25.00%) |
| occurrences (all)             | 0              | 0               | 1              |
| Ageusia                       |                |                 |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Dysgeusia                     |                |                 |                |

|                                      |                |                  |                |
|--------------------------------------|----------------|------------------|----------------|
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                    | 0              | 0                | 0              |
| Hypotonia                            |                |                  |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)                    | 0              | 1                | 0              |
| Blood and lymphatic system disorders |                |                  |                |
| Anaemia                              |                |                  |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 11 / 23 (47.83%) | 2 / 4 (50.00%) |
| occurrences (all)                    | 3              | 16               | 2              |
| Febrile neutropenia                  |                |                  |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 4 / 23 (17.39%)  | 1 / 4 (25.00%) |
| occurrences (all)                    | 0              | 4                | 1              |
| Leukocytosis                         |                |                  |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)                    | 0              | 1                | 0              |
| Leukopenia                           |                |                  |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 7 / 23 (30.43%)  | 1 / 4 (25.00%) |
| occurrences (all)                    | 1              | 10               | 1              |
| Lymphadenopathy                      |                |                  |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)                    | 0              | 2                | 0              |
| Neutropenia                          |                |                  |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 12 / 23 (52.17%) | 1 / 4 (25.00%) |
| occurrences (all)                    | 1              | 16               | 1              |
| Splenomegaly                         |                |                  |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)                    | 0              | 1                | 0              |
| Thrombocytopenia                     |                |                  |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 12 / 23 (52.17%) | 2 / 4 (50.00%) |
| occurrences (all)                    | 1              | 22               | 2              |
| Cytopenia                            |                |                  |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                    | 0              | 0                | 0              |
| Ear and labyrinth disorders          |                |                  |                |
| Ear haemorrhage                      |                |                  |                |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Vertigo                     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 2              | 0             |
| Eye disorders               |                |                |               |
| Cataract                    |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Dry eye                     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Erythema of eyelid          |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Eye haemorrhage             |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 2              | 0             |
| Eyelid oedema               |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Glaucoma                    |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Lacrimation increased       |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Macular degeneration        |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Visual acuity reduced       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Visual impairment           |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Hyphaema                    |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Photopsia                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gastrointestinal disorders  |                |                 |                |
| Abdominal pain              |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 4 / 23 (17.39%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 4               | 0              |
| Abdominal pain upper        |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Abnormal faeces             |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Anal haemorrhage            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Ascites                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Constipation                |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 6 / 23 (26.09%) | 2 / 4 (50.00%) |
| occurrences (all)           | 1              | 7               | 2              |
| Diarrhoea                   |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 6 / 23 (26.09%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 2              | 8               | 0              |
| Dry mouth                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dyspepsia                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dysphagia                   |                |                 |                |

|                               |                |                |                |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0              |
| Enterocolitis                 |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Faecaloma                     |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Flatulence                    |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 1              | 1              | 0              |
| Gastritis                     |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Gastrointestinal inflammation |                |                |                |
| subjects affected / exposed   | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 1              | 0              | 0              |
| Gingival bleeding             |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 1              | 0              |
| Gingival discolouration       |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Gingival pain                 |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Gingival swelling             |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Glossodynia                   |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0              |
| Haematochezia                 |                |                |                |
| subjects affected / exposed   | 0 / 5 (0.00%)  | 1 / 23 (4.35%) | 1 / 4 (25.00%) |
| occurrences (all)             | 0              | 1              | 1              |
| Haemorrhoids                  |                |                |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 2              | 0               | 0              |
| Hiatus hernia               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mouth haemorrhage           |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 3               | 1              |
| Mouth ulceration            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Nausea                      |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 7 / 23 (30.43%) | 2 / 4 (50.00%) |
| occurrences (all)           | 3              | 14              | 2              |
| Oesophagitis                |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Oral mucosal erythema       |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oral pain                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Periodontal disease         |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Proctalgia                  |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Rectal haemorrhage          |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Small intestine ulcer       |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Stomatitis                  |                |                 |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 5 (60.00%) | 5 / 23 (21.74%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 3              | 5               | 0              |
| Tongue coated               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tongue ulceration           |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Toothache                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Vomiting                    |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 6 / 23 (26.09%) | 1 / 4 (25.00%) |
| occurrences (all)           | 1              | 8               | 1              |
| Anal incontinence           |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Aphthous ulcer              |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Tongue discolouration       |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Abdominal discomfort        |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gastric ulcer               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gastrointestinal disorder   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Palatal disorder            |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tongue haemorrhage          |                |                 |                |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 1 / 23 (4.35%)<br>1 | 0 / 4 (0.00%)<br>0 |
| Hepatobiliary disorders                          |                    |                     |                    |
| Cholelithiasis                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic congestion                               |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic cyst                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatic lesion                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hepatomegaly                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 1 / 23 (4.35%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |
| Hyperbilirubinaemia                              |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 3 / 23 (13.04%)     | 1 / 4 (25.00%)     |
| occurrences (all)                                | 0                  | 4                   | 1                  |
| Hepatic steatosis                                |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Skin and subcutaneous tissue disorders           |                    |                     |                    |
| Alopecia   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 3 / 23 (13.04%)     | 2 / 4 (50.00%)     |
| occurrences (all)                                | 0                  | 3                   | 2                  |
| Blister  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Blood blister                                    |                    |                     |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 23 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Dermatitis atopic                                |                    |                     |                    |



|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dermatitis exfoliative      |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dry skin                    |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Erythema                    |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 1               | 0              |
| Haemorrhage subcutaneous    |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hyperhidrosis               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Night sweats                |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 3               | 1              |
| Pain of skin                |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Parapsoriasis               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Petechiae                   |                |                 |                |
| subjects affected / exposed | 2 / 5 (40.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 2              | 3               | 0              |
| Pruritus                    |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 2               | 1              |
| Psoriasis                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Purpura                     |                |                 |                |

|                             |               |                 |               |
|-----------------------------|---------------|-----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Rash                        |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 4 / 23 (17.39%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 5               | 0             |
| Skin erosion                |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Skin haemorrhage            |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Skin hyperpigmentation      |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Skin lesion                 |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Swelling face               |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Urticaria                   |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Eczema                      |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Ingrowing nail              |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Intertrigo                  |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Renal and urinary disorders |               |                 |               |
| Anuria                      |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |

|                             |               |                 |               |
|-----------------------------|---------------|-----------------|---------------|
| Bladder pain                |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Dysuria                     |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 3               | 0             |
| Glycosuria                  |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Haematuria                  |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 1               | 0             |
| Leukocyturia                |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Micturition disorder        |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Nephropathy                 |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Nocturia                    |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Pollakiuria                 |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Proteinuria                 |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Renal atrophy               |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Renal cyst                  |               |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 1               | 0             |

|   |                     |                      |                    |
|---|---------------------|----------------------|--------------------|
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Renal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Urethral haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Urethral pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 2 / 23 (8.70%)<br>2  | 0 / 4 (0.00%)<br>0 |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Endocrine disorders<br>Adrenal disorder<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 0 / 23 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 3 / 5 (60.00%)<br>3 | 3 / 23 (13.04%)<br>4 | 0 / 4 (0.00%)<br>0 |
| Arthritis   |                     |                      |                    |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 0               | 1              |
| Back pain                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 3               | 3              |
| Bone lesion                 |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Bone pain                   |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Flank pain                  |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Groin pain                  |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Joint swelling              |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Muscle spasms               |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Muscular weakness           |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 3               | 0              |
| Musculoskeletal pain        |                |                 |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Myalgia                     |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Myopathy                    |                |                 |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Osteoarthritis              |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Osteolysis                              |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Osteopenia                              |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Osteoporosis                            |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Pain in extremity                       |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 1 / 4 (25.00%) |
| occurrences (all)                       | 0              | 3               | 1              |
| Spinal osteoarthritis                   |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 1               | 0              |
| Infections and infestations             |                |                 |                |
| Bacterial infection                     |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Beta haemolytic streptococcal infection |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Bronchitis                              |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Candida infection                       |                |                 |                |
| subjects affected / exposed             | 1 / 5 (20.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 1              | 1               | 0              |
| Clostridium difficile infection         |                |                 |                |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)                       | 0              | 0               | 0              |
| Cystitis                                |                |                 |                |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Device related infection    |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 23 (4.35%) | 0 / 4 (0.00%) |
| occurrences (all)           | 1              | 1              | 0             |
| Diverticulitis              |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Enterococcal infection      |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Erysipelas                  |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Escherichia bacteraemia     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Escherichia infection       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Fungal infection            |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Fungal skin infection       |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Fusobacterium infection     |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Gingivitis                  |                |                |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Herpes simplex              |                |                |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Herpes virus infection      |                |                |               |

|                             |                |                 |               |
|-----------------------------|----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 23 (4.35%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 1              | 1               | 0             |
| Herpes zoster               |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 1               | 0             |
| Micrococcus infection       |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Nail bed infection          |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Nasopharyngitis             |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Oral candidiasis            |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Oral herpes                 |                |                 |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 3 / 23 (13.04%) | 0 / 4 (0.00%) |
| occurrences (all)           | 1              | 5               | 0             |
| Pharyngitis                 |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 4               | 0             |
| Pneumonia                   |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 3               | 0             |
| Pneumonia fungal            |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Pseudomonas infection       |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 2               | 0             |
| Sepsis                      |                |                 |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0              | 0               | 0             |
| Skin infection              |                |                 |               |



|                                    |                |                  |                |
|------------------------------------|----------------|------------------|----------------|
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Staphylococcal infection           |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Urinary tract infection            |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Urosepsis                          |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Osteomyelitis                      |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Post procedural infection          |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Soft tissue infection              |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 1                | 0              |
| Metabolism and nutrition disorders |                |                  |                |
| Acidosis                           |                |                  |                |
| subjects affected / exposed        | 1 / 5 (20.00%) | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 1              | 0                | 0              |
| Alkalosis                          |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Decreased appetite                 |                |                  |                |
| subjects affected / exposed        | 1 / 5 (20.00%) | 10 / 23 (43.48%) | 1 / 4 (25.00%) |
| occurrences (all)                  | 1              | 14               | 1              |
| Dehydration                        |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |
| Diabetes mellitus                  |                |                  |                |
| subjects affected / exposed        | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0              | 0                | 0              |

|                             |                |                  |                |
|-----------------------------|----------------|------------------|----------------|
| Hypercalcaemia              |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Hypercholesterolaemia       |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Hyperglycaemia              |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1                | 0              |
| Hyperkalaemia               |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Hypernatraemia              |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 23 (4.35%)   | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 1                | 2              |
| Hyperuricaemia              |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 3 / 23 (13.04%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 3                | 0              |
| Hypoalbuminaemia            |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 4 / 23 (17.39%)  | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 6                | 1              |
| Hypocalcaemia               |                |                  |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 6 / 23 (26.09%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 9                | 0              |
| Hypoglycaemia               |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 23 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0                | 0              |
| Hypokalaemia                |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 10 / 23 (43.48%) | 2 / 4 (50.00%) |
| occurrences (all)           | 0              | 17               | 4              |
| Hyponatraemia               |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)   | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 7                | 1              |
| Hypoproteinaemia            |                |                  |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 23 (8.70%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 2                | 0              |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Iron overload               |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Uraemic acidosis            |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Vitamin D deficiency        |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Fluid overload              |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 23 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 20 October 2008  | To allow for close cardiac monitoring of patients during the trial, additional Electrocardiogram (ECG) and troponin analyses were added. A formal safety analysis after the Phase I part of the trial and if necessary an updated benefit risk assessment was implemented. The Phase I part safety analysis was to be made available to all involved competent authorities and ethics committees. The blood sample for pharmacogenetic analysis was increased to 10 milliLiter (mL) to allow for different additives and different volumes in commercial tubes. The addition of further Pharmacokinetics (PK) analyses on volasertib metabolites, if applicable, was added to obtain further information on the PK of volasertib  |
| 11 August 2009   | The procedure was changed for allocation of patients in the Phase I part to treatment groups. This change in allocation for the Phase I part of the trial was implemented to avoid or shorten periods with stopped recruitment. Recruitment was to be stopped if the planned number of patients at a dose level was recruited in both schedules until all patients at that dose level finished the first treatment cycle. A non-randomised allocation of patients to treatment groups reduced the risk that the planned number of patients was recruited in both schedules at the same time. Changed dose escalation in Schedule B (volasertib monotherapy) to minimise the number of patients treated at suboptimal doses of volasertib. Change in details of packaging and labelling for Low-dose cytarabine (LDAC) used in the Phase II part of the trial. Details on serious adverse event (SAE) reporting changed to enhance comprehensibility of the procedure.       |
| 12 November 2009 | The procedure for allocating patients in the Phase I part to treatment schedules was changed. This change was implemented based on the first preliminary results that suggested an inferior clinical effect of volasertib monotherapy at the dose levels investigated at this point compared to the combination of volasertib and Low-dose cytarabine (LDAC). Screening for additional mutations and deregulated expression of genes was added to the planned cytogenetic and molecular genetic testing to allow the most up to date diagnostics in the trial. The sample volume of blood needed was adapted. The wording for the replacement of patients was considered misleading for the Phase II part of the trial so this was clarified. The address of the coordinating investigator was changed. The rules for pharmacodynamic investigations were changed, with the Progressive disease (PD) analysis being changed to being optional in Phase II part of the trial |
| 01 December 2010 | Details on exclusion of patients with QT interval corrected (QTc) prolongation were added to provide more accurate recommendations for the management of QTc interval prolongation and ventricular tachyarrhythmia  |
| 26 May 2011      | Details were added on timing and preparation of the clinical trial report (CTR) at the end of the trial. An early analysis of response to therapy was added to support internal strategic decisions/planning regarding future clinical trials.  |
| 20 March 2012    | Details on timing and preparation of the CTR were clarified.  |
| 23 July 2013     | Details on timing and preparation of the CTR were clarified.  |
| 14 October 2014  | The vial size of volasertib was changed to administer a dose of 350 milligram (mg) by the use of only 1 vial.   |

|                  |   |
|------------------|---|
| 12 January 2017  | Procedures and data collection were reduced to a minimum because the sponsor decided to discontinue volasertib development; however, patients with a clinical benefit could continue treatment. The sample size changed from about 143 to 177 enrolled (175 evaluable) to provide current and up-to-date information. |
| 07 February 2019 | Details on electronic data capture were updated.  |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported