



## Clinical trial results:

### A Phase 1b/2 Multi-Center, Open Label, Dose-Escalation Study To Determine The Maximum Tolerated Dose, Safety, And Efficacy Of Acy-1215 (Ricolinostat) In Combination With Pomalidomide And Low-Dose Dexamethasone In Patients With Relapsed-And Refractory Multiple Myeloma

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-002338-29   |
| Trial protocol           | IT GR            |
| Global end of trial date | 29 February 2024 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 27 February 2025 |
| First version publication date | 27 February 2025 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | ACE-MM-102 |
|-----------------------|------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bristol-Myers Squibb  |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170                                     |
| Public contact               | EU Study Start-Up Unit, Bristol-Myers Squibb,<br>Clinical.Trials@bms.com              |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb,<br>Clinical.Trials@bms.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 19 April 2024    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 29 February 2024 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 February 2024 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

Phase 1b:

To determine the maximum tolerated dose (MTD), or if not present, the recommended Phase 2 dose and schedule of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.

Phase 2:

To determine the efficacy of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone as treatment for patients with relapsed-and-refractory MM as assessed by overall response rate.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 March 2014 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 16        |
| Country: Number of subjects enrolled | Greece: 19        |
| Country: Number of subjects enrolled | Italy: 6          |
| Country: Number of subjects enrolled | United States: 62 |
| Worldwide total number of subjects   | 103               |
| EEA total number of subjects         | 25                |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 50 |
| From 65 to 84 years       | 52 |
| 85 years and over         | 1  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study consisted of Phase 1b (dose finding segment) part and Phase 2(dose expansion segment) part.

### Period 1

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

### Arms

|                              |                                  |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes                              |
| <b>Arm title</b>             | Phase 1b - ACY-1215 Dose Level 1 |

Arm description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ACY-1215     |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Oral liquid  |
| Routes of administration               | Oral use     |

Dosage and administration details:

160 mg/day on Days 1-21 of a 28-day cycle

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

Dosage and administration details:

40 mg PO for patients  $\leq 75$  years of age or 20 mg for patients  $> 75$  years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.

|  |              |
|--|--------------|
| Investigational medicinal product name | Pomalidomide |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

4 mg/day on Days 1-21 of a 28-day cycle

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Phase 1b - ACY-1215 Dose Level 3 |
|------------------|----------------------------------|

Arm description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

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

|   |                                 |
|---|---------------------------------|
| Investigational medicinal product name  | ACY-1215                        |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Oral liquid                     |
| Routes of administration  | Oral use                        |
| Dosage and administration details:<br>160 mg twice/day on Days 1-21 of a 28-day cycle   |                                 |
| Investigational medicinal product name  | Dexamethasone                   |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Tablet                          |
| Routes of administration  | Oral use                        |
| Dosage and administration details:<br>40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.  |                                 |
| Investigational medicinal product name  | Pomalidomide                    |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Capsule                         |
| Routes of administration  | Oral use                        |
| Dosage and administration details:<br>4 mg/day on Days 1-21 of a 28-day cycle   |                                 |
| <b>Arm title</b>  | Phase 2 - ACY-1215 Dose Level 1 |
| Arm description:<br>Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (≤75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle. |                                 |
| Arm type  | Experimental                    |
| Investigational medicinal product name  | ACY-1215                        |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Oral liquid                     |
| Routes of administration  | Oral use                        |
| Dosage and administration details:<br>160 mg/day on Days 1-21 of a 28-day cycle   |                                 |
| Investigational medicinal product name  | Dexamethasone                   |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Tablet                          |
| Routes of administration  | Oral use                        |
| Dosage and administration details:<br>40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.  |                                 |
| Investigational medicinal product name  | Pomalidomide                    |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Capsule                         |
| Routes of administration  | Oral use                        |
| Dosage and administration details:<br>4 mg/day on Days 1-21 of a 28-day cycle   |                                 |
| <b>Arm title</b>  | Phase 2 - ACY-1215 Dose Level 3 |

Arm description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ACY-1215     |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Oral liquid  |
| Routes of administration               | Oral use     |

Dosage and administration details:

160 mg twice/day on Days 1-21 of a 28-day cycle

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

Dosage and administration details:

40 mg PO for patients  $\leq 75$  years of age or 20 mg for patients  $> 75$  years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.

|  |              |
|--|--------------|
| Investigational medicinal product name | Pomalidomide |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

4 mg/day on Days 1-21 of a 28-day cycle

| Number of subjects in period 1 | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 |
|--------------------------------|----------------------------------|----------------------------------|---------------------------------|
| Started                        | 3                                | 4                                | 85                              |
| Efficacy evaluable population  | 3                                | 4                                | 77                              |
| Safety population              | 3                                | 4                                | 85                              |
| Completed                      | 0                                | 0                                | 0                               |
| Not completed                  | 3                                | 4                                | 85                              |
| Physician decision             | -                                | -                                | 3                               |
| Adverse event, non-fatal       | -                                | -                                | 15                              |
| Withdrawal by participant      | -                                | -                                | 8                               |
| Other reasons                  | -                                | -                                | 1                               |
| Progressive disease            | 3                                | 4                                | 57                              |
| Lost to follow-up              | -                                | -                                | 1                               |

| Number of subjects in period 1 | Phase 2 - ACY-1215 Dose Level 3 |
|--------------------------------|---------------------------------|
| Started                        | 11                              |
| Efficacy evaluable population  | 7                               |
| Safety population              | 11                              |

|                           |    |
|---------------------------|----|
| Completed                 | 0  |
| Not completed             | 11 |
| Physician decision        | -  |
| Adverse event, non-fatal  | 2  |
| Withdrawal by participant | 1  |
| Other reasons             | -  |
| Progressive disease       | 8  |
| Lost to follow-up         | -  |

## Baseline characteristics

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 1b - ACY-1215 Dose Level 1 |
|-----------------------|----------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 1b - ACY-1215 Dose Level 3 |
|-----------------------|----------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Phase 2 - ACY-1215 Dose Level 1 |
|-----------------------|---------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Phase 2 - ACY-1215 Dose Level 3 |
|-----------------------|---------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

| Reporting group values                    | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 |
|---|----------------------------------|----------------------------------|---------------------------------|
| Number of subjects                        | 3                                | 4                                | 85                              |
| Age Categorical<br>Units: Participants    |                                  |                                  |                                 |
| $\leq 18$ years                           | 0                                | 0                                | 0                               |
| Between 18 and 65 years                   | 2                                | 2                                | 42                              |
| $\geq 65$ years                           | 1                                | 2                                | 43                              |
| Age continuous<br>Units: years            |                                  |                                  |                                 |
| arithmetic mean                           | 62.0                             | 68.0                             | 64.6                            |
| standard deviation                        | $\pm 14.42$                      | $\pm 6.48$                       | $\pm 8.83$                      |
| Sex: Female, Male<br>Units: Participants  |                                  |                                  |                                 |
| Female                                    | 2                                | 1                                | 40                              |
| Male                                      | 1                                | 3                                | 45                              |
| Race (NIH/OMB)<br>Units: Subjects         |                                  |                                  |                                 |
| American Indian or Alaska Native          | 0                                | 0                                | 1                               |
| Asian                                     | 0                                | 0                                | 3                               |
| Native Hawaiian or Other Pacific Islander | 0                                | 0                                | 0                               |
| Black or African American                 | 0                                | 0                                | 7                               |
| White                                     | 3                                | 4                                | 72                              |
| More than one race                        | 0                                | 0                                | 0                               |
| Unknown or Not Reported                   | 0                                | 0                                | 2                               |
| Ethnicity (NIH/OMB)<br>Units: Subjects    |                                  |                                  |                                 |



|                         |   |   |    |
|-------------------------|---|---|----|
| Hispanic or Latino      | 0 | 0 | 1  |
| Not Hispanic or Latino  | 3 | 4 | 81 |
| Unknown or Not Reported | 0 | 0 | 3  |

| <b>Reporting group values</b>                | Phase 2 - ACY-1215<br>Dose Level 3 | Total |  |
|--|------------------------------------|-------|--|
| Number of subjects                           | 11                                 | 103   |  |
| Age Categorical<br>Units: Participants       |                                    |       |  |
| <=18 years                                   | 0                                  | 0     |  |
| Between 18 and 65 years                      | 4                                  | 50    |  |
| >=65 years                                   | 7                                  | 53    |  |
| Age continuous<br>Units: years               |                                    |       |  |
| arithmetic mean                              | 67.1                               |       |  |
| standard deviation                           | ± 8.81                             | -     |  |
| Sex: Female, Male<br>Units: Participants     |                                    |       |  |
| Female                                       | 4                                  | 47    |  |
| Male   | 7                                  | 56    |  |
| Race (NIH/OMB)<br>Units: Subjects            |                                    |       |  |
| American Indian or Alaska Native             | 0                                  | 1     |  |
| Asian  | 0                                  | 3     |  |
| Native Hawaiian or Other Pacific<br>Islander | 0                                  | 0     |  |
| Black or African American                    | 1                                  | 8     |  |
| White  | 10                                 | 89    |  |
| More than one race                           | 0                                  | 0     |  |
| Unknown or Not Reported                      | 0                                  | 2     |  |
| Ethnicity (NIH/OMB)<br>Units: Subjects       |                                    |       |  |
| Hispanic or Latino                           | 0                                  | 1     |  |
| Not Hispanic or Latino                       | 11                                 | 99    |  |
| Unknown or Not Reported                      | 0                                  | 3     |  |

## End points

### End points reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | Phase 1b - ACY-1215 Dose Level 1 |
| Reporting group description:<br>Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$ years) or 20 mg ( $> 75$ years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.   |                                  |
| Reporting group title  | Phase 1b - ACY-1215 Dose Level 3 |
| Reporting group description:<br>Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$ years) or 20 mg ( $> 75$ years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.  |                                  |
| Reporting group title  | Phase 2 - ACY-1215 Dose Level 1  |
| Reporting group description:<br>Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$ years) or 20 mg ( $> 75$ years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.   |                                  |
| Reporting group title  | Phase 2 - ACY-1215 Dose Level 3  |
| Reporting group description:<br>Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$ years) or 20 mg ( $> 75$ years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.  |                                  |
| Subject analysis set title   | Phase 1b - ACY-1215              |
| Subject analysis set type  | Sub-group analysis               |
| Subject analysis set description:<br>Participants received either 160 mg ACY-1215 once per day (Dose Level 1) or 160 mg ACY-1215 twice per day (Dose Level 3) and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$ years) or 20 mg ( $> 75$ years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle. |                                  |

### Primary: Maximum Tolerated Dose (MTD) of ACY-1215- Phase 1b

|   |   |
|---|---|
| End point title   | Maximum Tolerated Dose (MTD) of ACY-1215- Phase 1b <sup>[1]</sup> |
| End point description:<br>The maximum tolerated dose (MTD) was defined as the highest dose level at which no more than 1 of 6 patients experienced a dose-limiting toxicity (DLT) within the first 28-day cycle. If no more than 1 of these 6 patients experienced a DLT within the first 28-day cycle, then the last dose level enrolled to meet these criteria was identified as the recommended dose for the Phase 2 segment of the study. |   |
| End point type  | Primary   |
| End point timeframe:<br>From first dose until the end of Phase 1b (up to a maximum of approximately 50 weeks).  |   |

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Phase 1b - ACY-1215  |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 7                    |  |  |  |
| Units: mg/day               | 320                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Overall Response Rate (ORR) per Investigator - Phase 2

|                 |  |
|-----------------|--|
| End point title | Overall Response Rate (ORR) per Investigator - Phase 2 <sup>[2][3]</sup> |
|-----------------|--|

End point description:

Overall response rate (ORR) is defined as the percentage of participants with a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

sCR:

- No detectable myeloma cells in the bone marrow.
- Normal free light chain ratio.
- Absence of clonal cells in the bone marrow.

CR:

- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- Less than 5% plasma cells in the bone marrow.

VGPR:

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or
- At least a 90% reduction in serum M-protein plus urine M-protein level less than 100 mg per 24 hours.

PR:

- At least a 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by at least 90% or to less than 200 mg per 24 hours.
- For patients with non-secretory myeloma, a reduction of at least 50% in the size of soft tissue plasmacytomas is required.

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

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

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

Justification: Prespecified to be reported for Phase 2 only.

| End point values                 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |  |  |
|----------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type               | Reporting group                 | Reporting group                 |  |  |
| Number of subjects analysed      | 77                              | 7                               |  |  |
| Units: Percent of Participants   |                                 |                                 |  |  |
| number (confidence interval 95%) | 39.0 (28.0 to 50.8)             | 71.4 (29.0 to 96.3)             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response (TTR)

|                 |                        |
|-----------------|------------------------|
| End point title | Time to Response (TTR) |
|-----------------|------------------------|

End point description:

Time to response (TTR) was defined as the time from first dose of study treatment to the first documentation of response (either partial response (PR) or complete response (CR)).

CR:

- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- Less than 5% plasma cells in the bone marrow.

PR:

- At least a 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by at least 90% or to less than 200 mg per 24 hours.
- For patients with non-secretory myeloma, a reduction of at least 50% in the size of soft tissue plasmacytomas is required.

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

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

| End point values                       | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|--|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type                     | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed            | 2                                | 0 <sup>[4]</sup>                 | 30                              | 5                               |
| Units: Weeks                           |                                  |                                  |                                 |                                 |
| arithmetic mean (full range (min-max)) | 8.50 (4.1 to 12.9)               | ( to )                           | 10.83 (4.1 to 40.1)             | 12.96 (7.9 to 31.9)             |

Notes:

[4] - No responders in Ph1b at DL3

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DoR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Duration of Response (DoR) |
|-----------------|----------------------------|

End point description:

Duration of Response (DOR) was defined as the time from first partial response (PR) or complete response (CR) to the first documentation of progressive disease (PD) or death.

PR:

- $\geq 50\%$  reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by  $\geq 90\%$  or to less than 200 mg per 24 hours.
- For non-secretory myeloma, a reduction of  $\geq 50\%$  in size of soft tissue plasmacytomas.

CR:

- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- $< 5\%$  plasma cells in the bone marrow.

PD:

- Increase of 25% or more from nadir in serum M-protein, absolute increase of  $\geq 0.5$  g/dL.
- Increase of 25% or more from nadir in 24-hour urinary M-protein, absolute increase of  $\geq 200$  mg/24 hours.
- Increase of 25% or more in the percentage of bone marrow plasma cells, absolute increase of  $\geq 10\%$ .

Calculated using Kaplan-Meier estimates.

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

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

| End point values                 | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|----------------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type               | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed      | 2                                | 0 <sup>[5]</sup>                 | 30                              | 5                               |
| Units: Weeks                     |                                  |                                  |                                 |                                 |
| median (confidence interval 95%) | 20.10 (4.10 to 36.10)            | ( to )                           | 30.30 (13.10 to 43.10)          | 62.75 (54.75 to 121.6)          |

Notes:

[5] - No responders in Ph1b at DL3

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression (TTP)

|                 |                           |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

Time to progression (TTP) was defined as the time from the date of first dose to the date of first documentation of progressive disease (PD).

PD:

- Increase of 25% or more from nadir in serum M-protein, absolute increase of  $\geq 0.5$  g/dL.
- Increase of 25% or more from nadir in 24-hour urinary M-protein, absolute increase of  $\geq 200$  mg/24 hours.
- Increase of 25% or more in the percentage of bone marrow plasma cells, absolute increase of  $\geq 10\%$ .
- New bone lesions or soft tissue plasmacytomas or increase size of existing bone lesions or soft tissue plasmacytomas.
- Hypercalcemia attributed to myeloma.

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

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

| End point values                       | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|--|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type                     | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed            | 3                                | 4                                | 77                              | 7                               |
| Units: Weeks                           |                                  |                                  |                                 |                                 |
| arithmetic mean (full range (min-max)) | 22.43 (8.1 to 48.9)              | 6.20 (4.1 to 8.1)                | 29.82 (3.9 to 169.1)            | 83.22 (7.7 to 183.1)            |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression-free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

Progression-free survival (PFS) was defined as the time from first dose of study treatment to the first

documentation of progressive disease (PD) or death from any cause during study

PD:

- Increase of 25% or more from nadir in serum M-protein, absolute increase of  $\geq 0.5$  g/dL.
- Increase of 25% or more from nadir in 24-hour urinary M-protein, absolute increase of  $\geq 200$  mg/24 hours.
- Increase of 25% or more in the percentage of bone marrow plasma cells, absolute increase of  $\geq 10\%$ .
- New bone lesions or soft tissue plasmacytomas or increase size of existing bone lesions or soft tissue plasmacytomas.
- Hypercalcemia attributed to myeloma.

Calculated using Kaplan-Meier estimates.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months). |           |

| End point values                 | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|----------------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type               | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed      | 3                                | 4                                | 77                              | 7                               |
| Units: Weeks                     |                                  |                                  |                                 |                                 |
| median (confidence interval 95%) | 22.43 (8.10 to 48.90)            | 6.30 (4.35 to 8.05)              | 20.00 (9.10 to 41.60)           | 62.70 (19.90 to 99.90)          |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate (ORR) per Central Adjudication Committee

|                 |  |
|-----------------|--|
| End point title | Overall Response Rate (ORR) per Central Adjudication Committee |
|-----------------|--|

End point description:

Overall response rate (ORR) is defined as the percentage of participants with a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

sCR:

- No detectable myeloma cells in the bone marrow.
- Normal free light chain ratio.
- Absence of clonal cells in the bone marrow.

CR:

- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- Less than 5% plasma cells in the bone marrow.

VGPR:

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or
- At least a 90% reduction in serum M-protein plus urine M-protein level less than 100 mg per 24 hours.

PR:

- At least a 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by at least 90% or to less than 200 mg per 24 hours.
- For patients with non-secretory myeloma, a reduction of at least 50% in the size of soft tissue plasmacytomas is required

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

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause

(up to approximately 120 months).

| End point values                 | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|----------------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type               | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed      | 0 <sup>[6]</sup>                 | 0 <sup>[7]</sup>                 | 0 <sup>[8]</sup>                | 0 <sup>[9]</sup>                |
| Units: Percent of Participants   |                                  |                                  |                                 |                                 |
| number (confidence interval 95%) | ( to )                           | ( to )                           | ( to )                          | ( to )                          |

Notes:

[6] - Data not collected

[7] - Data not collected

[8] - Data not collected

[9] - Data not collected

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Adverse Events (AEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants with Adverse Events (AEs) |
|-----------------|--|

End point description:

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. Graded according to NCI CTCAE (Version 4.03) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

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

End point timeframe:

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

| End point values            | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|-----------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type          | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed | 3                                | 4                                | 85                              | 11                              |
| Units: Participants         | 3                                | 4                                | 82                              | 11                              |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Serious Adverse Events (SAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Serious Adverse Events (SAEs) |
|-----------------|---|

---

**End point description:**

A serious adverse event (SAE) is defined as any adverse event (AE) occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the participant is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay).
- Results in persistent or significant disability/incapacity (a substantial disruption of the participant's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Graded according to NCI CTCAE (Version 4) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

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

---

**End point timeframe:**

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

---

| End point values            | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|-----------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type          | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed | 3                                | 4                                | 85                              | 11                              |
| Units: Participants         | 0                                | 2                                | 37                              | 7                               |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of Participants with Adverse Events (AEs) Leading to Discontinuation**

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|                 |   |
|-----------------|---|
| End point title | Number of Participants with Adverse Events (AEs) Leading to Discontinuation |
|-----------------|---|

---

**End point description:**

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. Graded according to NCI CTCAE (Version 4.03) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

---

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

---

**End point timeframe:**

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

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| End point values            | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|-----------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type          | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed | 3                                | 4                                | 85                              | 11                              |
| Units: Participants         |                                  |                                  |                                 |                                 |
| ACY-1215                    | 0                                | 0                                | 13                              | 1                               |
| Pomalidomide                | 0                                | 0                                | 13                              | 1                               |
| Dexamethasone               | 0                                | 0                                | 16                              | 1                               |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events (AEs) Related to Study Drug

|                 |  |
|-----------------|--|
| End point title | Number of Participants with Adverse Events (AEs) Related to Study Drug |
|-----------------|--|

End point description:

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. Graded according to NCI CTCAE (Version 4.03) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

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

End point timeframe:

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

| End point values            | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 | Phase 2 - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 |
|-----------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type          | Reporting group                  | Reporting group                  | Reporting group                 | Reporting group                 |
| Number of subjects analysed | 3                                | 4                                | 85                              | 11                              |
| Units: Participants         |                                  |                                  |                                 |                                 |
| ACY-1215                    | 1                                | 4                                | 63                              | 9                               |
| Pomalidomide                | 3                                | 4                                | 62                              | 11                              |
| Dexamethasone               | 2                                | 3                                | 57                              | 9                               |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Levels of ACY-1215 and Pomalidomide - Phase 1b

|                 |   |
|-----------------|---|
| End point title | Plasma Levels of ACY-1215 and Pomalidomide - Phase 1b <sup>[10]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Cycle 1 day 1, Cycle 1 Day 2, Cycle 1 Day 8

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: Prespecified to be reported for Phase 1b only.

| End point values            | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 |  |  |
|-----------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed | 0 <sup>[11]</sup>                | 0 <sup>[12]</sup>                |  |  |
| Units: ng/L                 |                                  |                                  |  |  |
| ACY-1215<br>Pomalidomide    |                                  |                                  |  |  |

Notes:

[11] - Data not collected

[12] - Data not collected

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Anti-Drug Antibodies (ADA) - Phase 1b

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Anti-Drug Antibodies (ADA) - Phase 1b <sup>[13]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Cycle 1 day 1, Cycle 1 Day 2, Cycle 1 Day 8

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: Prespecified to be reported for Phase 1b only.

| End point values            | Phase 1b - ACY-1215 Dose Level 1 | Phase 1b - ACY-1215 Dose Level 3 |  |  |
|-----------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed | 0 <sup>[14]</sup>                | 0 <sup>[15]</sup>                |  |  |
| Units: Participants         |                                  |                                  |  |  |
| ACY-1215<br>Pomalidomide    |                                  |                                  |  |  |

Notes:

[14] - Data not collected

[15] - Data not collected

### Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs and Non-Serious AEs were assessed from first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks).

Adverse event reporting additional description:

Serious Adverse Events and Non-Serious Adverse Events represents all participants that received at least 1 dose of study medication.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 1b - ACY-1215 Dose Level 1 |
|-----------------------|----------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Phase 2 - ACY-1215 Dose Level 3 |
|-----------------------|---------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Phase 2 -ACY-1215 Dose Level 1 |
|-----------------------|--------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 1b - ACY-1215 Dose Level 3 |
|-----------------------|----------------------------------|

Reporting group description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg ( $\leq 75$  years) or 20 mg ( $> 75$  years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

| Serious adverse events  | Phase 1b - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 | Phase 2 -ACY-1215 Dose Level 1 |
|---|----------------------------------|---------------------------------|--------------------------------|
| Total subjects affected by serious adverse events                   |                                  |                                 |                                |
| subjects affected / exposed   | 0 / 3 (0.00%)                    | 7 / 11 (63.64%)                 | 37 / 85 (43.53%)               |
| number of deaths (all causes)                                       | 2                                | 3                               | 39                             |
| number of deaths resulting from adverse events                      |                                  |                                 |                                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |                                 |                                |
| Squamous cell carcinoma   |                                  |                                 |                                |
| subjects affected / exposed   | 0 / 3 (0.00%)                    | 1 / 11 (9.09%)                  | 3 / 85 (3.53%)                 |
| occurrences causally related to treatment / all                     | 0 / 0                            | 0 / 1                           | 0 / 3                          |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0                           | 0 / 0                          |
| Cholangiocarcinoma  |                                  |                                 |                                |

|  |               |                |                |
|--|---------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Basal cell carcinoma                                 |               |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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 lymphocytic leukaemia                          |               |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Vascular disorders                                   |               |                |                |
| Aortic aneurysm                                      |               |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |               |                |                |
| Chest pain   |               |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 0 / 85 (0.00%) |
| 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 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Sudden death   |               |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 1          |
| Immune system disorders                              |               |                |                |
| Drug hypersensitivity                                |               |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 0 / 85 (0.00%) |
| 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 |               |                |                |
| Respiratory failure                             |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 1          |
| Respiratory distress                            |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 85 (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          |
| Hypoxia   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Dyspnoea  |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Chronic obstructive pulmonary disease           |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia aspiration                            |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |               |                |                |
| Delirium  |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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 / 3 (0.00%) | 0 / 11 (0.00%) | 0 / 85 (0.00%) |
| 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>                                 |               |                |                |
| White blood cell count decreased                      |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all            | 0 / 0         | 0 / 0          | 0 / 0          |
| <b>Injury, poisoning and procedural complications</b> |               |                |                |
| Femoral neck fracture                                 |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all            | 0 / 0         | 0 / 0          | 0 / 0          |
| Femur fracture  |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all            | 0 / 0         | 0 / 0          | 0 / 0          |
| Hip fracture  |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all            | 0 / 0         | 0 / 0          | 0 / 0          |
| Lumbar vertebral fracture                             |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all            | 0 / 0         | 0 / 0          | 0 / 0          |
| <b>Cardiac disorders</b>                              |               |                |                |
| Atrial fibrillation                                   |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0         | 0 / 1          | 2 / 3          |
| deaths causally related to treatment / all            | 0 / 0         | 0 / 0          | 0 / 0          |
| Coronary artery occlusion                             |               |                |                |
| subjects affected / exposed                           | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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 congestive                      |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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 chronic                         |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 85 (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          |
| Bradycardia                                     |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Atrioventricular block complete                 |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |               |                |                |
| Cerebrovascular accident                        |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Spinal cord compression                         |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Radiculopathy                                   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Embolic stroke                                  |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |               |                |                |



|   |               |                |                |
|---|---------------|----------------|----------------|
| Febrile neutropenia                             |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 4 / 4          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Thrombocytopenia                                |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Neutropenia                                     |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |               |                |                |
| Nausea  |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Vomiting  |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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                     |               |                |                |
| Haematuria                                      |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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 failure                                   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Renal failure acute                             |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

|   |               |                |                |
|---|---------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders |               |                |                |
| Pathological fracture                           |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Bone pain                                       |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Muscular weakness                               |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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                     |               |                |                |
| Bronchitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cellulitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Corona virus infection                          |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Escherichia sepsis                              |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Haemophilus infection                           |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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 viral                                 |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Influenza                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Lower respiratory tract infection               |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Meningitis bacterial                            |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 1 / 1          |
| Pneumonia                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 6 / 85 (7.06%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           | 2 / 7          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 1          |
| Pneumonia parainfluenzae viral                  |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (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          |
| Implant site infection                          |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Respiratory tract infection                     |               |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Sepsis  |               |                 |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 1 / 2          |
| Septic shock                                    |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 2          |
| Streptococcal bacteraemia                       |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 3          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Urosepsis                                       |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| 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              |               |                |                |
| Hypercalcaemia                                  |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Dehydration                                     |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Decreased appetite                              |               |                |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Tumour lysis syndrome                           |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hypokalaemia                                    |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

| Serious adverse events  | Phase 1b - ACY-1215 Dose Level 3 |  |  |
|---|----------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                  |  |  |
| subjects affected / exposed   | 2 / 4 (50.00%)                   |  |  |
| number of deaths (all causes)                                       | 1                                |  |  |
| number of deaths resulting from adverse events                      |                                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |  |  |
| Squamous cell carcinoma   |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                            |  |  |
| deaths causally related to treatment / all                          | 0 / 0                            |  |  |
| Cholangiocarcinoma  |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                            |  |  |
| deaths causally related to treatment / all                          | 0 / 0                            |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Basal cell carcinoma                                 |                |  |  |
| subjects affected / exposed                          | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Acute lymphocytic leukaemia                          |                |  |  |
| subjects affected / exposed                          | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| Aortic aneurysm                                      |                |  |  |
| subjects affected / exposed                          | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Chest pain   |                |  |  |
| subjects affected / exposed                          | 1 / 4 (25.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General physical health deterioration                |                |  |  |
| subjects affected / exposed                          | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Sudden death   |                |  |  |
| subjects affected / exposed                          | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Drug hypersensitivity                                |                |  |  |
| subjects affected / exposed                          | 1 / 4 (25.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders      |                |  |  |
| Respiratory failure                                  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory distress                            |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypoxia   |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Chronic obstructive pulmonary disease           |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia aspiration                            |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Delirium  |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Confusional state                               |                |  |  |
| subjects affected / exposed                     | 1 / 4 (25.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |

|   |               |  |  |
|---|---------------|--|--|
| White blood cell count decreased<br>subjects affected / exposed | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Injury, poisoning and procedural<br>complications               |               |  |  |
| Femoral neck fracture<br>subjects affected / exposed            | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Femur fracture<br>subjects affected / exposed                   | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Hip fracture<br>subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Lumbar vertebral fracture<br>subjects affected / exposed        | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Cardiac disorders   |               |  |  |
| Atrial fibrillation<br>subjects affected / exposed              | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Coronary artery occlusion<br>subjects affected / exposed        | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |
| Cardiac failure congestive<br>subjects affected / exposed       | 0 / 4 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0         |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0         |  |  |



|   |               |  |  |
|---|---------------|--|--|
| Cardiac failure chronic                         |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Bradycardia                                     |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Atrioventricular block complete                 |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Nervous system disorders                        |               |  |  |
| Cerebrovascular accident                        |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Spinal cord compression                         |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Radiculopathy                                   |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Embolic stroke                                  |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Blood and lymphatic system disorders            |               |  |  |
| Febrile neutropenia                             |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |

|   |               |  |  |
|---|---------------|--|--|
| Thrombocytopenia                                |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Neutropenia                                     |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Gastrointestinal disorders                      |               |  |  |
| Nausea  |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Vomiting  |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Renal and urinary disorders                     |               |  |  |
| Haematuria                                      |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Renal failure                                   |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Renal failure acute                             |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Musculoskeletal and connective tissue disorders |               |  |  |
| Pathological fracture                           |               |  |  |

|   |               |  |  |
|---|---------------|--|--|
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Bone pain                                       |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Muscular weakness                               |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Infections and infestations                     |               |  |  |
| Bronchitis                                      |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Cellulitis                                      |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Corona virus infection                          |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Escherichia sepsis                              |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Haemophilus infection                           |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Pneumonia viral                                 |               |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Influenza                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Meningitis bacterial                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 4 (25.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia parainfluenzae viral                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Implant site infection                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Respiratory tract infection                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis  |                |  |  |  |

|   |               |  |  |
|---|---------------|--|--|
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Septic shock                                    |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Streptococcal bacteraemia                       |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Upper respiratory tract infection               |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Urinary tract infection                         |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Urosepsis                                       |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Metabolism and nutrition disorders              |               |  |  |
| Hypercalcaemia                                  |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Dehydration                                     |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Decreased appetite                              |               |  |  |

|   |               |  |  |
|---|---------------|--|--|
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Hyperkalaemia                                   |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Hyponatraemia                                   |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Tumour lysis syndrome                           |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Hypokalaemia                                    |               |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |

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

| <b>Non-serious adverse events</b>                                   | Phase 1b - ACY-1215 Dose Level 1 | Phase 2 - ACY-1215 Dose Level 3 | Phase 2 -ACY-1215 Dose Level 1 |
|---|----------------------------------|---------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events               |                                  |                                 |                                |
| subjects affected / exposed   | 3 / 3 (100.00%)                  | 11 / 11 (100.00%)               | 79 / 85 (92.94%)               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |                                 |                                |
| Skin papilloma  |                                  |                                 |                                |
| subjects affected / exposed   | 0 / 3 (0.00%)                    | 1 / 11 (9.09%)                  | 0 / 85 (0.00%)                 |
| occurrences (all)   | 0                                | 1                               | 0                              |
| Vascular disorders  |                                  |                                 |                                |
| Peripheral coldness   |                                  |                                 |                                |
| subjects affected / exposed   | 0 / 3 (0.00%)                    | 1 / 11 (9.09%)                  | 0 / 85 (0.00%)                 |
| occurrences (all)   | 0                                | 1                               | 0                              |
| Flushing  |                                  |                                 |                                |

|  |                |                 |                  |
|--|----------------|-----------------|------------------|
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 5 / 85 (5.88%)   |
| occurrences (all)                                    | 0              | 0               | 5                |
| Hypertension   |                |                 |                  |
| subjects affected / exposed                          | 2 / 3 (66.67%) | 4 / 11 (36.36%) | 2 / 85 (2.35%)   |
| occurrences (all)                                    | 4              | 7               | 3                |
| Hypotension  |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 3 / 85 (3.53%)   |
| occurrences (all)                                    | 0              | 2               | 3                |
| Orthostatic hypotension                              |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                                    | 0              | 1               | 0                |
| Aortic arteriosclerosis                              |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                                    | 0              | 1               | 0                |
| General disorders and administration site conditions |                |                 |                  |
| Instillation site pain                               |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 4 / 85 (4.71%)   |
| occurrences (all)                                    | 0              | 2               | 4                |
| Asthenia   |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 7 / 85 (8.24%)   |
| occurrences (all)                                    | 0              | 0               | 8                |
| Chest discomfort                                     |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)                                    | 0              | 1               | 1                |
| Chest pain   |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 4 / 85 (4.71%)   |
| occurrences (all)                                    | 0              | 0               | 4                |
| Chills   |                |                 |                  |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)                                    | 0              | 1               | 4                |
| Fatigue  |                |                 |                  |
| subjects affected / exposed                          | 2 / 3 (66.67%) | 8 / 11 (72.73%) | 49 / 85 (57.65%) |
| occurrences (all)                                    | 2              | 13              | 59               |
| Feeling jittery                                      |                |                 |                  |

|   |               |                 |                  |
|---|---------------|-----------------|------------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0             | 1               | 0                |
| Influenza like illness                          |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 5 / 85 (5.88%)   |
| occurrences (all)                               | 0             | 0               | 5                |
| Local swelling                                  |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 4 / 85 (4.71%)   |
| occurrences (all)                               | 0             | 3               | 4                |
| Oedema peripheral                               |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 13 / 85 (15.29%) |
| occurrences (all)                               | 0             | 2               | 20               |
| Pyrexia   |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 18 / 85 (21.18%) |
| occurrences (all)                               | 0             | 1               | 26               |
| Vessel puncture site bruise                     |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0             | 0               | 0                |
| Oedema  |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 5 / 85 (5.88%)   |
| occurrences (all)                               | 0             | 0               | 5                |
| Immune system disorders                         |               |                 |                  |
| Hypogammaglobulinaemia                          |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0             | 1               | 0                |
| Respiratory, thoracic and mediastinal disorders |               |                 |                  |
| Pleural effusion                                |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0             | 1               | 0                |
| Acute respiratory failure                       |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0             | 1               | 0                |
| Bronchospasm                                    |               |                 |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 11 (0.00%)  | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0             | 0               | 0                |
| Oropharyngeal pain                              |               |                 |                  |



|                             |               |                 |                  |
|-----------------------------|---------------|-----------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 8 / 85 (9.41%)   |
| occurrences (all)           | 0             | 2               | 9                |
| Nasal congestion            |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 11 (27.27%) | 4 / 85 (4.71%)   |
| occurrences (all)           | 0             | 3               | 4                |
| Lung infiltration           |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0             | 1               | 0                |
| Hiccups                     |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)           | 0             | 1               | 4                |
| Epistaxis                   |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 8 / 85 (9.41%)   |
| occurrences (all)           | 0             | 1               | 8                |
| Dyspnoea exertional         |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 9 / 85 (10.59%)  |
| occurrences (all)           | 0             | 2               | 10               |
| Dyspnoea                    |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 11 (27.27%) | 8 / 85 (9.41%)   |
| occurrences (all)           | 0             | 4               | 8                |
| Cough                       |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 11 (27.27%) | 15 / 85 (17.65%) |
| occurrences (all)           | 0             | 4               | 21               |
| Productive cough            |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 5 / 85 (5.88%)   |
| occurrences (all)           | 0             | 1               | 5                |
| Pulmonary hypertension      |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0             | 1               | 0                |
| Rhinorrhoea                 |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 3 / 85 (3.53%)   |
| occurrences (all)           | 0             | 2               | 3                |
| Sinus congestion            |               |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%)  | 2 / 85 (2.35%)   |
| occurrences (all)           | 0             | 1               | 2                |
| Throat irritation           |               |                 |                  |

|  |                    |                     |                     |
|--|--------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 1 / 11 (9.09%)<br>2 | 4 / 85 (4.71%)<br>4 |
| Psychiatric disorders                            |                    |                     |                     |
| Confusional state                                |                    |                     |                     |
| subjects affected / exposed                      | 1 / 3 (33.33%)     | 0 / 11 (0.00%)      | 3 / 85 (3.53%)      |
| occurrences (all)                                | 2                  | 0                   | 3                   |
| Anxiety  |                    |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 2 / 11 (18.18%)     | 2 / 85 (2.35%)      |
| occurrences (all)                                | 0                  | 3                   | 2                   |
| Delirium   |                    |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 11 (0.00%)      | 0 / 85 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                   |
| Insomnia   |                    |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 3 / 11 (27.27%)     | 16 / 85 (18.82%)    |
| occurrences (all)                                | 0                  | 4                   | 16                  |
| Mood altered                                     |                    |                     |                     |
| subjects affected / exposed                      | 1 / 3 (33.33%)     | 2 / 11 (18.18%)     | 4 / 85 (4.71%)      |
| occurrences (all)                                | 2                  | 2                   | 4                   |
| Depression                                       |                    |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 11 (0.00%)      | 6 / 85 (7.06%)      |
| occurrences (all)                                | 0                  | 0                   | 6                   |
| Investigations                                   |                    |                     |                     |
| Neutrophil count decreased                       |                    |                     |                     |
| subjects affected / exposed                      | 2 / 3 (66.67%)     | 3 / 11 (27.27%)     | 12 / 85 (14.12%)    |
| occurrences (all)                                | 4                  | 8                   | 27                  |
| Alanine aminotransferase increased               |                    |                     |                     |
| subjects affected / exposed                      | 1 / 3 (33.33%)     | 0 / 11 (0.00%)      | 7 / 85 (8.24%)      |
| occurrences (all)                                | 1                  | 0                   | 8                   |
| Aspartate aminotransferase increased             |                    |                     |                     |
| subjects affected / exposed                      | 2 / 3 (66.67%)     | 0 / 11 (0.00%)      | 6 / 85 (7.06%)      |
| occurrences (all)                                | 2                  | 0                   | 7                   |
| Blood alkaline phosphatase increased             |                    |                     |                     |
| subjects affected / exposed                      | 1 / 3 (33.33%)     | 0 / 11 (0.00%)      | 4 / 85 (4.71%)      |
| occurrences (all)                                | 1                  | 0                   | 4                   |
| Blood cholesterol increased                      |                    |                     |                     |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed                    | 1 / 3 (33.33%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)                              | 1               | 1               | 0              |
| Blood creatinine increased                     |                 |                 |                |
| subjects affected / exposed                    | 0 / 3 (0.00%)   | 2 / 11 (18.18%) | 7 / 85 (8.24%) |
| occurrences (all)                              | 0               | 2               | 10             |
| Blood glucose increased                        |                 |                 |                |
| subjects affected / exposed                    | 0 / 3 (0.00%)   | 1 / 11 (9.09%)  | 1 / 85 (1.18%) |
| occurrences (all)                              | 0               | 1               | 1              |
| Gamma-glutamyltransferase increased            |                 |                 |                |
| subjects affected / exposed                    | 1 / 3 (33.33%)  | 0 / 11 (0.00%)  | 0 / 85 (0.00%) |
| occurrences (all)                              | 1               | 0               | 0              |
| Haematocrit decreased                          |                 |                 |                |
| subjects affected / exposed                    | 0 / 3 (0.00%)   | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)                              | 0               | 1               | 0              |
| Haemoglobin decreased                          |                 |                 |                |
| subjects affected / exposed                    | 3 / 3 (100.00%) | 3 / 11 (27.27%) | 0 / 85 (0.00%) |
| occurrences (all)                              | 3               | 4               | 0              |
| Lymphocyte count decreased                     |                 |                 |                |
| subjects affected / exposed                    | 0 / 3 (0.00%)   | 1 / 11 (9.09%)  | 2 / 85 (2.35%) |
| occurrences (all)                              | 0               | 2               | 3              |
| Platelet count decreased                       |                 |                 |                |
| subjects affected / exposed                    | 1 / 3 (33.33%)  | 4 / 11 (36.36%) | 6 / 85 (7.06%) |
| occurrences (all)                              | 3               | 5               | 8              |
| Weight decreased                               |                 |                 |                |
| subjects affected / exposed                    | 0 / 3 (0.00%)   | 2 / 11 (18.18%) | 3 / 85 (3.53%) |
| occurrences (all)                              | 0               | 2               | 3              |
| White blood cell count decreased               |                 |                 |                |
| subjects affected / exposed                    | 2 / 3 (66.67%)  | 4 / 11 (36.36%) | 4 / 85 (4.71%) |
| occurrences (all)                              | 3               | 10              | 8              |
| Injury, poisoning and procedural complications |                 |                 |                |
| Fall   |                 |                 |                |
| subjects affected / exposed                    | 0 / 3 (0.00%)   | 2 / 11 (18.18%) | 2 / 85 (2.35%) |
| occurrences (all)                              | 0               | 2               | 2              |
| Compression fracture                           |                 |                 |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Periorbital contusion       |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Scar                        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Spinal compression fracture |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Procedural pain             |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%) |
| occurrences (all)           | 0              | 1               | 1              |
| Cardiac disorders           |                |                 |                |
| Atrial fibrillation         |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%) |
| occurrences (all)           | 0              | 1               | 3              |
| Cardiac failure congestive  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Palpitations                |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Sinus bradycardia           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 3               | 0              |
| Sinus tachycardia           |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 1 / 85 (1.18%) |
| occurrences (all)           | 1              | 0               | 1              |
| Tricuspid valve disease     |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Nervous system disorders    |                |                 |                |
| Hypoaesthesia               |                |                 |                |

|                               |                |                 |                  |
|-------------------------------|----------------|-----------------|------------------|
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 3 / 85 (3.53%)   |
| occurrences (all)             | 0              | 1               | 3                |
| Headache                      |                |                 |                  |
| subjects affected / exposed   | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 7 / 85 (8.24%)   |
| occurrences (all)             | 1              | 0               | 7                |
| Dysgeusia                     |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 11 / 85 (12.94%) |
| occurrences (all)             | 0              | 1               | 11               |
| Dizziness postural            |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 2 / 85 (2.35%)   |
| occurrences (all)             | 0              | 1               | 2                |
| Dizziness                     |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 11 / 85 (12.94%) |
| occurrences (all)             | 0              | 2               | 12               |
| Balance disorder              |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)             | 0              | 1               | 1                |
| Memory impairment             |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)             | 0              | 1               | 4                |
| Vlith nerve paralysis         |                |                 |                  |
| subjects affected / exposed   | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 0 / 85 (0.00%)   |
| occurrences (all)             | 1              | 0               | 0                |
| Tremor                        |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 10 / 85 (11.76%) |
| occurrences (all)             | 0              | 0               | 10               |
| Syncope                       |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 2 / 85 (2.35%)   |
| occurrences (all)             | 0              | 1               | 2                |
| Somnolence                    |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 1 / 85 (1.18%)   |
| occurrences (all)             | 0              | 0               | 1                |
| Peripheral sensory neuropathy |                |                 |                  |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 1 / 85 (1.18%)   |
| occurrences (all)             | 0              | 0               | 1                |
| Neuropathy peripheral         |                |                 |                  |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 1 / 11 (9.09%)<br>1 | 4 / 85 (4.71%)<br>4 |
| Blood and lymphatic system disorders             |                     |                     |                     |
| Anaemia  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 2 / 11 (18.18%)     | 31 / 85 (36.47%)    |
| occurrences (all)                                | 0                   | 3                   | 41                  |
| Febrile neutropenia                              |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 1 / 85 (1.18%)      |
| occurrences (all)                                | 0                   | 1                   | 1                   |
| Lymphadenopathy                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 0 / 85 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Lymphopenia                                      |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 3 / 85 (3.53%)      |
| occurrences (all)                                | 0                   | 2                   | 6                   |
| Neutropenia                                      |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 5 / 11 (45.45%)     | 29 / 85 (34.12%)    |
| occurrences (all)                                | 0                   | 6                   | 59                  |
| Thrombocytopenia                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 17 / 85 (20.00%)    |
| occurrences (all)                                | 0                   | 1                   | 23                  |
| Leukopenia                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 2 / 11 (18.18%)     | 3 / 85 (3.53%)      |
| occurrences (all)                                | 0                   | 4                   | 5                   |
| Ear and labyrinth disorders                      |                     |                     |                     |
| Deafness   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 1 / 85 (1.18%)      |
| occurrences (all)                                | 0                   | 1                   | 1                   |
| Ear pain   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 0 / 85 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Tinnitus   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 3 (0.00%)       | 1 / 11 (9.09%)      | 1 / 85 (1.18%)      |
| occurrences (all)                                | 0                   | 1                   | 1                   |
| Eye disorders                                    |                     |                     |                     |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Cataract                    |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 3               | 0              |
| Diplopia                    |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Dry eye                     |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%) |
| occurrences (all)           | 0              | 1               | 1              |
| Ectropion                   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Lacrimation increased       |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%) |
| occurrences (all)           | 0              | 1               | 1              |
| Vision blurred              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 3 / 85 (3.53%) |
| occurrences (all)           | 0              | 1               | 3              |
| Dacryostenosis acquired     |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Gastrointestinal disorders  |                |                 |                |
| Flatulence                  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 3 / 85 (3.53%) |
| occurrences (all)           | 0              | 2               | 3              |
| Abdominal distension        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 7 / 85 (8.24%) |
| occurrences (all)           | 0              | 2               | 8              |
| Abdominal pain              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 7 / 85 (8.24%) |
| occurrences (all)           | 0              | 1               | 7              |
| Abdominal pain upper        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 6 / 85 (7.06%) |
| occurrences (all)           | 0              | 0               | 7              |
| Aphthous stomatitis         |                |                 |                |

|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Constipation                |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 14 / 85 (16.47%) |
| occurrences (all)           | 0              | 2               | 16               |
| Diarrhoea                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 6 / 11 (54.55%) | 32 / 85 (37.65%) |
| occurrences (all)           | 0              | 14              | 47               |
| Dyspepsia                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 4 / 85 (4.71%)   |
| occurrences (all)           | 0              | 2               | 4                |
| Dysphagia                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 3 / 85 (3.53%)   |
| occurrences (all)           | 0              | 1               | 3                |
| Gastrointestinal disorder   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Gingival pain               |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Hypoaesthesia oral          |                |                 |                  |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 1              | 0               | 0                |
| Nausea                      |                |                 |                  |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 11 (27.27%) | 19 / 85 (22.35%) |
| occurrences (all)           | 2              | 3               | 22               |
| Oral disorder               |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)           | 0              | 1               | 1                |
| Oral pain                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)           | 0              | 1               | 1                |
| Sensitivity of teeth        |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Vomiting                    |                |                 |                  |



|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed            | 1 / 3 (33.33%) | 1 / 11 (9.09%)  | 9 / 85 (10.59%) |
| occurrences (all)                      | 2              | 2               | 10              |
| Gastrooesophageal reflux disease       |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 2 / 85 (2.35%)  |
| occurrences (all)                      | 0              | 1               | 2               |
| Skin and subcutaneous tissue disorders |                |                 |                 |
| Night sweats                           |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 5 / 85 (5.88%)  |
| occurrences (all)                      | 0              | 0               | 5               |
| Pruritus                               |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 2 / 11 (18.18%) | 2 / 85 (2.35%)  |
| occurrences (all)                      | 1              | 2               | 3               |
| Actinic keratosis                      |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Alopecia                               |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 2 / 85 (2.35%)  |
| occurrences (all)                      | 0              | 2               | 2               |
| Dry skin                               |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Ecchymosis                             |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Erythema multiforme                    |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)  |
| occurrences (all)                      | 0              | 1               | 0               |
| Hair growth abnormal                   |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)  |
| occurrences (all)                      | 0              | 1               | 0               |
| Hair texture abnormal                  |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)  |
| occurrences (all)                      | 0              | 1               | 0               |
| Hyperhidrosis                          |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 3 / 11 (27.27%) | 2 / 85 (2.35%)  |
| occurrences (all)                      | 0              | 3               | 2               |

|   |                |                |                  |
|---|----------------|----------------|------------------|
| Rash  |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 11 (0.00%) | 10 / 85 (11.76%) |
| occurrences (all)                               | 0              | 0              | 17               |
| Rash maculo-papular                             |                |                |                  |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 11 (9.09%) | 1 / 85 (1.18%)   |
| occurrences (all)                               | 1              | 1              | 1                |
| Skin disorder                                   |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |
| Skin lesion                                     |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |
| Swelling face                                   |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 1 / 85 (1.18%)   |
| occurrences (all)                               | 0              | 1              | 1                |
| Renal and urinary disorders                     |                |                |                  |
| Renal failure                                   |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 1 / 85 (1.18%)   |
| occurrences (all)                               | 0              | 1              | 1                |
| Renal failure acute                             |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 11 (0.00%) | 2 / 85 (2.35%)   |
| occurrences (all)                               | 0              | 0              | 2                |
| Endocrine disorders                             |                |                |                  |
| Cushingoid                                      |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 2 / 85 (2.35%)   |
| occurrences (all)                               | 0              | 1              | 2                |
| Musculoskeletal and connective tissue disorders |                |                |                  |
| Bursitis  |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |
| Tenosynovitis                                   |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |
| Bone disorder                                   |                |                |                  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 11 (9.09%) | 0 / 85 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0                |

|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| Back pain                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 3 / 11 (27.27%) | 13 / 85 (15.29%) |
| occurrences (all)           | 0              | 4               | 15               |
| Arthropathy                 |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Arthritis                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Arthralgia                  |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 13 / 85 (15.29%) |
| occurrences (all)           | 0              | 2               | 15               |
| Joint swelling              |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 11 (18.18%) | 2 / 85 (2.35%)   |
| occurrences (all)           | 0              | 2               | 2                |
| Muscle spasms               |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 3 / 11 (27.27%) | 17 / 85 (20.00%) |
| occurrences (all)           | 0              | 3               | 18               |
| Muscular weakness           |                |                 |                  |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 11 (18.18%) | 9 / 85 (10.59%)  |
| occurrences (all)           | 1              | 2               | 9                |
| Musculoskeletal chest pain  |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)           | 0              | 1               | 4                |
| Musculoskeletal discomfort  |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 0              | 1               | 0                |
| Neck pain                   |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)           | 0              | 1               | 4                |
| Osteoarthritis              |                |                 |                  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)           | 0              | 1               | 1                |
| Osteoporosis                |                |                 |                  |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 0 / 85 (0.00%)   |
| occurrences (all)           | 1              | 0               | 0                |

|   |                     |                      |                        |
|---|---------------------|----------------------|------------------------|
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  | 9 / 85 (10.59%)<br>11  |
| Rotator cuff syndrome<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  | 0 / 85 (0.00%)<br>0    |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0  | 2 / 11 (18.18%)<br>2 | 11 / 85 (12.94%)<br>12 |
| Infections and infestations   |                     |                      |                        |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 3 (0.00%)<br>0  | 2 / 11 (18.18%)<br>4 | 3 / 85 (3.53%)<br>3    |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  | 3 / 85 (3.53%)<br>3    |
| Herpes simplex<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 3 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  | 0 / 85 (0.00%)<br>0    |
| Herpes virus infection<br>subjects affected / exposed<br>occurrences (all)            | 0 / 3 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  | 0 / 85 (0.00%)<br>0    |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0  | 2 / 11 (18.18%)<br>2 | 3 / 85 (3.53%)<br>4    |
| Localised infection<br>subjects affected / exposed<br>occurrences (all)               | 0 / 3 (0.00%)<br>0  | 1 / 11 (9.09%)<br>1  | 3 / 85 (3.53%)<br>3    |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0  | 8 / 85 (9.41%)<br>8    |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 3 / 11 (27.27%)<br>9 | 21 / 85 (24.71%)<br>31 |
| Urinary tract infection   |                     |                      |                        |

|   |                |                 |                  |
|---|----------------|-----------------|------------------|
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 6 / 85 (7.06%)   |
| occurrences (all)                       | 0              | 1               | 7                |
| Viral upper respiratory tract infection |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)                       | 0              | 1               | 1                |
| Metabolism and nutrition disorders      |                |                 |                  |
| Decreased appetite                      |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 3 / 11 (27.27%) | 9 / 85 (10.59%)  |
| occurrences (all)                       | 0              | 3               | 10               |
| Dehydration                             |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 2 / 85 (2.35%)   |
| occurrences (all)                       | 0              | 1               | 3                |
| Hypercalcaemia                          |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)                       | 0              | 1               | 4                |
| Hyperglycaemia                          |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 7 / 85 (8.24%)   |
| occurrences (all)                       | 0              | 1               | 9                |
| Hyperkalaemia                           |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 1 / 85 (1.18%)   |
| occurrences (all)                       | 0              | 1               | 1                |
| Hypermagnesaemia                        |                |                 |                  |
| subjects affected / exposed             | 1 / 3 (33.33%) | 0 / 11 (0.00%)  | 1 / 85 (1.18%)   |
| occurrences (all)                       | 1              | 0               | 1                |
| Hyperuricaemia                          |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 4 / 85 (4.71%)   |
| occurrences (all)                       | 0              | 1               | 5                |
| Hypocalcaemia                           |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 5 / 85 (5.88%)   |
| occurrences (all)                       | 0              | 1               | 5                |
| Hypoglycaemia                           |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 1 / 11 (9.09%)  | 0 / 85 (0.00%)   |
| occurrences (all)                       | 0              | 1               | 0                |
| Hypokalaemia                            |                |                 |                  |
| subjects affected / exposed             | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 11 / 85 (12.94%) |
| occurrences (all)                       | 0              | 0               | 14               |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Hypomagnesaemia             |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 3 / 85 (3.53%) |
| occurrences (all)           | 0              | 0               | 4              |
| Hyponatraemia               |                |                 |                |
| subjects affected / exposed | 2 / 3 (66.67%) | 3 / 11 (27.27%) | 7 / 85 (8.24%) |
| occurrences (all)           | 2              | 4               | 9              |
| Hypophosphataemia           |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 11 (18.18%) | 7 / 85 (8.24%) |
| occurrences (all)           | 1              | 7               | 7              |
| Polydipsia                  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 11 (0.00%)  | 0 / 85 (0.00%) |
| occurrences (all)           | 0              | 0               | 0              |

|   |                                  |  |  |
|---|----------------------------------|--|--|
| <b>Non-serious adverse events</b>                                   | Phase 1b - ACY-1215 Dose Level 3 |  |  |
| Total subjects affected by non-serious adverse events               |                                  |  |  |
| subjects affected / exposed   | 4 / 4 (100.00%)                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |  |  |
| Skin papilloma  |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences (all)   | 0                                |  |  |
| Vascular disorders  |                                  |  |  |
| Peripheral coldness   |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences (all)   | 0                                |  |  |
| Flushing  |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences (all)   | 0                                |  |  |
| Hypertension  |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences (all)   | 0                                |  |  |
| Hypotension   |                                  |  |  |
| subjects affected / exposed   | 1 / 4 (25.00%)                   |  |  |
| occurrences (all)   | 1                                |  |  |
| Orthostatic hypotension   |                                  |  |  |
| subjects affected / exposed   | 0 / 4 (0.00%)                    |  |  |
| occurrences (all)   | 0                                |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Aortic arteriosclerosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  |  |  |
| General disorders and administration<br>site conditions                     |                     |  |  |
| Instillation site pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 4 (25.00%)<br>1 |  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 4 (25.00%)<br>1 |  |  |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)        | 0 / 4 (0.00%)<br>0  |  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 4 (25.00%)<br>1 |  |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 4 (25.00%)<br>1 |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 4 (50.00%)<br>3 |  |  |
| Feeling jittery<br>subjects affected / exposed<br>occurrences (all)         | 0 / 4 (0.00%)<br>0  |  |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  |  |  |
| Local swelling<br>subjects affected / exposed<br>occurrences (all)          | 0 / 4 (0.00%)<br>0  |  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)       | 0 / 4 (0.00%)<br>0  |  |  |
| Pyrexia   |                     |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 4 (25.00%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Vessel puncture site bruise                     |                |  |  |
| subjects affected / exposed                     | 1 / 4 (25.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Oedema  |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Immune system disorders                         |                |  |  |
| Hypogammaglobulinaemia                          |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Acute respiratory failure                       |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Bronchospasm                                    |                |  |  |
| subjects affected / exposed                     | 1 / 4 (25.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Oropharyngeal pain                              |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Nasal congestion                                |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Lung infiltration                               |                |  |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Hiccups   |                |  |  |
| subjects affected / exposed                     | 1 / 4 (25.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Epistaxis                                       |                |  |  |



|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 4 (50.00%) |  |  |
| occurrences (all)           | 3              |  |  |
| Dyspnoea exertional         |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Dyspnoea                    |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Cough                       |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Productive cough            |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pulmonary hypertension      |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Rhinorrhoea                 |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Sinus congestion            |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Throat irritation           |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Psychiatric disorders       |                |  |  |
| Confusional state           |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Anxiety                     |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Delirium                    |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| Insomnia                             |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Mood altered                         |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Depression                           |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Investigations                       |                |  |  |
| Neutrophil count decreased           |                |  |  |
| subjects affected / exposed          | 1 / 4 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Alanine aminotransferase increased   |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Aspartate aminotransferase increased |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Blood alkaline phosphatase increased |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Blood cholesterol increased          |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Blood creatinine increased           |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Blood glucose increased              |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Gamma-glutamyltransferase increased  |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Haematocrit decreased                |                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Haemoglobin decreased                          |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Lymphocyte count decreased                     |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Platelet count decreased                       |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Weight decreased                               |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| White blood cell count decreased               |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Injury, poisoning and procedural complications |                |  |  |
| Fall   |                |  |  |
| subjects affected / exposed                    | 1 / 4 (25.00%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Compression fracture                           |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Periorbital contusion                          |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Scar   |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Spinal compression fracture                    |                |  |  |
| subjects affected / exposed                    | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Procedural pain                                |                |  |  |

|  |                    |  |  |
|--|--------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 |  |  |
| Cardiac disorders                                |                    |  |  |
| Atrial fibrillation                              |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Cardiac failure congestive                       |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Palpitations                                     |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Sinus bradycardia                                |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Sinus tachycardia                                |                    |  |  |
| subjects affected / exposed                      | 1 / 4 (25.00%)     |  |  |
| occurrences (all)                                | 1                  |  |  |
| Tricuspid valve disease                          |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Nervous system disorders                         |                    |  |  |
| Hypoaesthesia                                    |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Headache   |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Dysgeusia  |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Dizziness postural                               |                    |  |  |
| subjects affected / exposed                      | 0 / 4 (0.00%)      |  |  |
| occurrences (all)                                | 0                  |  |  |
| Dizziness  |                    |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed          | 1 / 4 (25.00%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Balance disorder                     |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Memory impairment                    |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Vlth nerve paralysis                 |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Tremor                               |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Syncope                              |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Somnolence                           |                |  |  |
| subjects affected / exposed          | 1 / 4 (25.00%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Peripheral sensory neuropathy        |                |  |  |
| subjects affected / exposed          | 1 / 4 (25.00%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Neuropathy peripheral                |                |  |  |
| subjects affected / exposed          | 1 / 4 (25.00%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood and lymphatic system disorders |                |  |  |
| Anaemia                              |                |  |  |
| subjects affected / exposed          | 2 / 4 (50.00%) |  |  |
| occurrences (all)                    | 4              |  |  |
| Febrile neutropenia                  |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Lymphadenopathy                      |                |  |  |
| subjects affected / exposed          | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 4 (0.00%)<br>0  |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 4 (25.00%)<br>1 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 4 (25.00%)<br>1 |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 4 (0.00%)<br>0  |  |  |
| Ear and labyrinth disorders<br>Deafness<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  |  |  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 4 (0.00%)<br>0  |  |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 4 (0.00%)<br>0  |  |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)               | 0 / 4 (0.00%)<br>0  |  |  |
| Diplopia<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 4 (0.00%)<br>0  |  |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 4 (0.00%)<br>0  |  |  |
| Ectropion<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 4 (0.00%)<br>0  |  |  |
| Lacrimation increased   |                     |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                            | 0 / 4 (0.00%)<br>0   |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)          | 1 / 4 (25.00%)<br>1  |  |  |
| Dacryostenosis acquired<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0   |  |  |
| Gastrointestinal disorders  |                      |  |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0   |  |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)    | 0 / 4 (0.00%)<br>0   |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)          | 2 / 4 (50.00%)<br>2  |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)    | 0 / 4 (0.00%)<br>0   |  |  |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)     | 0 / 4 (0.00%)<br>0   |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)            | 3 / 4 (75.00%)<br>3  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | 4 / 4 (100.00%)<br>4 |  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 4 (0.00%)<br>0   |  |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 4 (0.00%)<br>0   |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Gastrointestinal disorder              |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Gingival pain                          |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Hypoaesthesia oral                     |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Nausea                                 |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Oral disorder                          |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Oral pain                              |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Sensitivity of teeth                   |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Vomiting                               |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Gastrooesophageal reflux disease       |                |  |  |
| subjects affected / exposed            | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Skin and subcutaneous tissue disorders |                |  |  |
| Night sweats                           |                |  |  |
| subjects affected / exposed            | 1 / 4 (25.00%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Pruritus                               |                |  |  |
| subjects affected / exposed            | 1 / 4 (25.00%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Actinic keratosis                      |                |  |  |



|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Alopecia                    |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Dry skin                    |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Ecchymosis                  |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Erythema multiforme         |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hair growth abnormal        |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hair texture abnormal       |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hyperhidrosis               |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Rash                        |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Rash maculo-papular         |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Skin disorder               |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Skin lesion                 |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Swelling face               |                |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  |  |  |
| Renal and urinary disorders<br>Renal failure<br>subjects affected / exposed<br>occurrences (all)                | 0 / 4 (0.00%)<br>0  |  |  |
| Renal failure acute<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>2 |  |  |
| Endocrine disorders<br>Cushingoid<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 4 (0.00%)<br>0  |  |  |
| Musculoskeletal and connective tissue disorders<br>Bursitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  |  |  |
| Tenosynovitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  |  |  |
| Bone disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  |  |  |
| Arthropathy<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  |  |  |
| Arthritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  |  |  |
| Joint swelling  |                     |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Muscle spasms               |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Muscular weakness           |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Musculoskeletal chest pain  |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Musculoskeletal discomfort  |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Neck pain                   |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Osteoarthritis              |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Osteoporosis                |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Pain in extremity           |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Rotator cuff syndrome       |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Bone pain                   |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Infections and infestations |                |  |  |
| Bronchitis                  |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Gastroenteritis                         |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Herpes simplex                          |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Herpes virus infection                  |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Influenza                               |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Localised infection                     |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Pneumonia                               |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Upper respiratory tract infection       |                |  |  |
| subjects affected / exposed             | 1 / 4 (25.00%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Urinary tract infection                 |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Viral upper respiratory tract infection |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Metabolism and nutrition disorders      |                |  |  |
| Decreased appetite                      |                |  |  |
| subjects affected / exposed             | 0 / 4 (0.00%)  |  |  |
| occurrences (all)                       | 0              |  |  |
| Dehydration                             |                |  |  |
| subjects affected / exposed             | 1 / 4 (25.00%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Hypercalcaemia                          |                |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hyperglycaemia              |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hyperkalaemia               |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 3              |  |  |
| Hypermagnesaemia            |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hyperuricaemia              |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hypocalcaemia               |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Hypoglycaemia               |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hypokalaemia                |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 2              |  |  |
| Hypomagnesaemia             |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hyponatraemia               |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hypophosphataemia           |                |  |  |
| subjects affected / exposed | 0 / 4 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Polydipsia                  |                |  |  |
| subjects affected / exposed | 1 / 4 (25.00%) |  |  |
| occurrences (all)           | 1              |  |  |



**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 09 February 2016 | Protocol version.<br>Clerical change in Study Personnel.<br>Clarification for Duration of Survival Follow-up |

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported