



## Clinical trial results:

**A phase Ib, multi-center, open-label, dose-escalation study of oral panobinostat (PAN) when administered in combination with oral lenalidomide and dexamethasone in adult patients with multiple myeloma**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2006-007030-35   |
| Trial protocol           | IT               |
| Global end of trial date | 08 November 2017 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 24 November 2018 |
| First version publication date | 24 November 2018 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLBH589B2206 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00532675 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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                       | 08 November 2017 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 08 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To determine the maximum tolerated dose (MTD) of panobinostat (PAN) when used in combination with a fixed dose of lenalidomide (Revlimid®) and dexamethasone

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 22 August 2008 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Australia: 18    |
| Country: Number of subjects enrolled | United States: 7 |
| Country: Number of subjects enrolled | France: 5        |
| Country: Number of subjects enrolled | Spain: 16        |
| Worldwide total number of subjects   | 46               |
| EEA total number of subjects         | 21               |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |    |
|----------------------|----|
| Adults (18-64 years) | 32 |
| From 65 to 84 years  | 14 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

46 patients were enrolled in this study and were assigned treatment.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Core 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>             | PAN 5 mg |

Arm description:

PAN 5 mg in combination with lenalidomide and dexamethasone

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Panobinostat  |
| Investigational medicinal product code | LBH589        |
| Other name                             | LBH589        |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

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

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

|  |              |
|--|--------------|
| <b>Arm title</b>   | PAN 10 mg    |
| Arm description:   |              |
| Pan 10 mg in combination with lenalidomide and dexamethasone |              |
| Arm type   | Experimental |

|  |               |
|--|---------------|
| Investigational medicinal product name | Panobinostat  |
| Investigational medicinal product code | LBH589        |
| Other name                             | LBH589        |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

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

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | PAN 20 mg |
|------------------|-----------|

Arm description:

PAN 20 mg in combination with lenalidomide and dexamethasone

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Panobinostat  |
| Investigational medicinal product code | LBH589        |
| Other name                             | LBH589        |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

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

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

|  |               |
|--|---------------|
| <b>Arm title</b>   | Pan 25 mg     |
| Arm description:<br>PAN 25 mg in combination with lenalidomide and dexamethasone |               |
| Arm type   | Experimental  |
| Investigational medicinal product name   | Panobinostat  |
| Investigational medicinal product code   | LBH589        |
| Other name   | LBH589        |
| Pharmaceutical forms   | Capsule, hard |
| Routes of administration   | Oral use      |

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

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

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

| <b>Number of subjects in period 1</b> | PAN 5 mg | PAN 10 mg | PAN 20 mg |
|---------------------------------------|----------|-----------|-----------|
| Started                               | 8        | 8         | 21        |
| Completed                             | 0        | 0         | 0         |
| Not completed                         | 8        | 8         | 21        |
| Abnormal laboratory value(s)          | -        | 1         | -         |
| Consent withdrawn by subject          | 2        | 1         | 3         |
| Adverse event, non-fatal              | 3        | 3         | 8         |
| Death                                 | -        | -         | 4         |
| Disease Progression                   | 3        | 3         | 5         |
| Protocol deviation                    | -        | -         | 1         |

| <b>Number of subjects in period 1</b> | Pan 25 mg |
|---------------------------------------|-----------|
| Started                               | 9         |
| Completed                             | 0         |
| Not completed                         | 9         |
| Abnormal laboratory value(s)          | -         |

|                              |   |
|------------------------------|---|
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal     | 4 |
| Death                        | - |
| Disease Progression          | 4 |
| Protocol deviation           | - |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | PAN 5 mg  |
| Reporting group description:<br>PAN 5 mg in combination with lenalidomide and dexamethasone  |           |
| Reporting group title  | PAN 10 mg |
| Reporting group description:<br>Pan 10 mg in combination with lenalidomide and dexamethasone |           |
| Reporting group title  | PAN 20 mg |
| Reporting group description:<br>PAN 20 mg in combination with lenalidomide and dexamethasone |           |
| Reporting group title  | Pan 25 mg |
| Reporting group description:<br>PAN 25 mg in combination with lenalidomide and dexamethasone |           |

| Reporting group values  | PAN 5 mg | PAN 10 mg | PAN 20 mg |
|---|----------|-----------|-----------|
| Number of subjects  | 8        | 8         | 21        |
| Age categorical<br>Units: Subjects  |          |           |           |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |          |           |           |
| Age continuous<br>Units: years  |          |           |           |
| arithmetic mean   | 64.9     | 60.6      | 59.1      |
| standard deviation  | ± 8.54   | ± 5.66    | ± 10.56   |
| Gender categorical<br>Units: Subjects   |          |           |           |
| Female  | 1        | 2         | 9         |
| Male  | 7        | 6         | 12        |

| Reporting group values   | Pan 25 mg | Total            |  |
|--|-----------|------------------|--|
| Number of subjects   | 9         | 46               |  |
| Age categorical<br>Units: Subjects   |           |                  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months) |           | 0<br>0<br>0<br>0 |  |



|                           |         |    |  |
|---------------------------|---------|----|--|
| Children (2-11 years)     |         | 0  |  |
| Adolescents (12-17 years) |         | 0  |  |
| Adults (18-64 years)      |         | 0  |  |
| From 65-84 years          |         | 0  |  |
| 85 years and over         |         | 0  |  |
| Age continuous            |         |    |  |
| Units: years              |         |    |  |
| arithmetic mean           | 56.1    |    |  |
| standard deviation        | ± 10.84 | -  |  |
| Gender categorical        |         |    |  |
| Units: Subjects           |         |    |  |
| Female                    | 5       | 17 |  |
| Male                      | 4       | 29 |  |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | PAN 5 mg  |
| Reporting group description:<br>PAN 5 mg in combination with lenalidomide and dexamethasone  |           |
| Reporting group title  | PAN 10 mg |
| Reporting group description:<br>Pan 10 mg in combination with lenalidomide and dexamethasone |           |
| Reporting group title  | PAN 20 mg |
| Reporting group description:<br>PAN 20 mg in combination with lenalidomide and dexamethasone |           |
| Reporting group title  | Pan 25 mg |
| Reporting group description:<br>PAN 25 mg in combination with lenalidomide and dexamethasone |           |

### Primary: Maximum Therapeutic Dose (MTD) of Panobinostat in combination with a fixed dose of lenalidomide and dexamethasone

|   |  |
|---|--|
| End point title   | Maximum Therapeutic Dose (MTD) of Panobinostat in combination with a fixed dose of lenalidomide and dexamethasone <sup>[1]</sup> |
| End point description:<br>After a total of 46 patients had been enrolled into the dose escalation phase, it was concluded that the dosing regimen and schedule needed to be changed for the combination used in this study, based on a review of the accrued safety data and evolution of medical practice on usage of dexamethasone. It was decided that recommended dosing regimen and schedule for this combination would be better implemented in a new study, rather than in a complex protocol amendment. Hence, this study was stopped without determining the MTD, and the dose expansion phase of the study was not initiated. |  |
| End point type  | Primary  |
| End point timeframe:<br>24 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: After a total of 46 subjects had been enrolled into the dose escalation phase, it was concluded that the dosing regimen and schedule needed to be changed for the combination used in this study, based on a review of the accrued safety data and evolution of medical practice on usage of dexamethasone. It was decided that recommended dosing regimen and schedule for this combination would be better implemented in a new study, rather than in a complex protocol amendment. The study stopped enrollment.

| End point values            | PAN 5 mg         | PAN 10 mg        | PAN 20 mg        | Pan 25 mg        |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed | 0 <sup>[2]</sup> | 0 <sup>[3]</sup> | 0 <sup>[4]</sup> | 0 <sup>[5]</sup> |
| Units: patients             |                  |                  |                  |                  |

#### Notes:

[2] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated

[3] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated

[4] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated

[5] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response (OR) per investigator's assessment by dose level of Panobinostat

|  |   |
|--|---|
| End point title  | Overall Response (OR) per investigator's assessment by dose level of Panobinostat |
| End point description:<br>Patients with confirmed best overall response = Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR)+ Partial Response (PR) were summarized on the Full Analysis Set (FAS). All 46 enrolled patients received at least one dose of study treatment; they were therefore included in the FAS. |   |
| End point type   | Secondary   |
| End point timeframe:<br>24 weeks   |   |

| End point values            | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8               | 8               | 21              | 9               |
| Units: patients             | 6               | 1               | 8               | 4               |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OR as per investigator's assessment for patients with measurable disease at baseline by dose level of Panobinostat

|   |  |
|---|--|
| End point title   | OR as per investigator's assessment for patients with measurable disease at baseline by dose level of Panobinostat |
| End point description:<br>Patients with confirmed best overall response as per investigator's assessment for patients with measurable disease = Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR)+ Partial Response (PR) were summarized on the Full Analysis Set (FAS). Best confirmed overall response was analyzed by patients with measurable disease at baseline as per the International Myeloma Working Group criteria (IMWG)specified for serum M protein, urine M protein, FLC level and bone marrow plasma cell percentage. All 46 enrolled patients received at least one dose of study treatment; they were therefore included in the FAS. |  |
| End point type  | Secondary  |
| End point timeframe:<br>24 weeks  |  |

| <b>End point values</b>     | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7               | 8               | 19              | 8               |
| Units: patients             | 5               | 1               | 7               | 4               |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OR as per investigator's assessment for relapsed-and-refractory patients by dose level of Panobinostat

|                 |  |
|-----------------|--|
| End point title | OR as per investigator's assessment for relapsed-and-refractory patients by dose level of Panobinostat |
|-----------------|--|

End point description:

Patients with confirmed best overall response (OR) as per investigator's assessment for relapsed and refractory patients = Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR)+ Partial Response (PR) were summarized on the Full Analysis Set (FAS). All 46 enrolled patients received at least one dose of study treatment; they were therefore included in the FAS.

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

End point timeframe:

24 weeks

| <b>End point values</b>     | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5               | 6               | 13              | 6               |
| Units: patients             | 4               | 0               | 4               | 2               |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Summary statistics of AUCinf for Panobinostat on Day 1

|                 |  |
|-----------------|--|
| End point title | Summary statistics of AUCinf for Panobinostat on Day 1 |
|-----------------|--|

End point description:

Area Under the Curve from 0 to infinity (AUCinf) for Panobinostat on Day 1  
Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations.

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

End point timeframe:

Day 1

| End point values                     | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 8               | 8               | 21              | 9               |
| Units: ng·h/mL                       |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 22.79 (± 25.1)  | 37.52 (± 34.1)  | 90.85 (± 44.4)  | 117.55 (± 43.7) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary statistics of AUClast for Panobinostat on Day 1

|  |   |
|--|---|
| End point title  | Summary statistics of AUClast for Panobinostat on Day 1 |
| End point description:   |   |
| Area Under the Curve from 0 to the time of the last quantifiable concentration; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Day 1  |   |

| End point values                     | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 8               | 8               | 21              | 9               |
| Units: ng·h/mL                       |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 10.14 (± 8.6)   | 31.38 (± 31.2)  | 75.93 (± 41.9)  | 102.53 (± 38.7) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary statistics of Cmax for Panobinostat on Day 1

|   |  |
|---|--|
| End point title   | Summary statistics of Cmax for Panobinostat on Day 1 |
| End point description:  |  |
| Maximum observed concentration (Cmax) is the peak serum concentration of a therapeutic drug after administration; and is used to determine the rate and extent of drug absorption; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Day 1   |  |

| End point values                     | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 8               | 8               | 21              | 9               |
| Units: ng/mL                         |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 1.87 (± 0.8)    | 7.89 (± 5.8)    | 13.91 (± 9.2)   | 20.03 (± 10.09) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary statistics of Tmax for Panobinostat on Day 1

|   |  |
|---|--|
| End point title   | Summary statistics of Tmax for Panobinostat on Day 1 |
| End point description:<br>Tmax = Time of occurrence of Cmax, Cmax is the peak serum concentration of a therapeutic drug after administration; and is used to determine the rate and extent of drug absorption; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Day 1   |  |

| End point values              | PAN 5 mg            | PAN 10 mg           | PAN 20 mg           | Pan 25 mg           |
|-------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type            | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed   | 8                   | 8                   | 21                  | 9                   |
| Units: hours                  |                     |                     |                     |                     |
| median (full range (min-max)) | 1.26 (0.75 to 4.00) | 1.25 (0.50 to 3.00) | 1.00 (0.42 to 2.50) | 1.00 (0.50 to 3.00) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary statistics of T1/2 for Panobinostat on Day 1

|  |  |
|--|--|
| End point title  | Summary statistics of T1/2 for Panobinostat on Day 1 |
| End point description:<br>t 1/2 = Terminal elimination half-life; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Day 1  |  |

| <b>End point values</b>              | PAN 5 mg        | PAN 10 mg       | PAN 20 mg       | Pan 25 mg       |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 8               | 8               | 21              | 9               |
| Units: hours                         |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 15.35 (± 27.3)  | 4.40 (± 2.5)    | 11.51 (± 4.7)   | 13.57 (± 5.4)   |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | PAN 5 mg |
|-----------------------|----------|

Reporting group description:

PAN 5 mg

|                       |           |
|-----------------------|-----------|
| Reporting group title | PAN 10 mg |
|-----------------------|-----------|

Reporting group description:

PAN 10 mg

|                       |           |
|-----------------------|-----------|
| Reporting group title | PAN 20 mg |
|-----------------------|-----------|

Reporting group description:

PAN 20 mg

|                       |           |
|-----------------------|-----------|
| Reporting group title | PAN 25 mg |
|-----------------------|-----------|

Reporting group description:

PAN 25 mg

| Serious adverse events  | PAN 5 mg       | PAN 10 mg      | PAN 20 mg        |
|---|----------------|----------------|------------------|
| Total subjects affected by serious adverse events                   |                |                |                  |
| subjects affected / exposed   | 3 / 8 (37.50%) | 5 / 8 (62.50%) | 18 / 21 (85.71%) |
| number of deaths (all causes)                                       | 0              | 0              | 6                |
| number of deaths resulting from adverse events                      | 0              | 0              | 2                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                  |
| Metastases to soft tissue   |                |                |                  |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0            |
| Squamous cell carcinoma   |                |                |                  |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0            |
| Vascular disorders  |                |                |                  |



|  |                |               |                |
|--|----------------|---------------|----------------|
| Deep vein thrombosis                                 |                |               |                |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Orthostatic hypotension                              |                |               |                |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Phlebitis  |                |               |                |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Thrombophlebitis superficial                         |                |               |                |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| General disorders and administration site conditions |                |               |                |
| Asthenia   |                |               |                |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 2 / 4          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Fatigue  |                |               |                |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| General physical health deterioration                |                |               |                |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Multiple organ dysfunction syndrome                  |                |               |                |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 1 / 1          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Non-cardiac chest pain                          |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 8          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Aspiration                                      |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cough   |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea exertional                             |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary haemorrhage                           |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |               |                |                 |
|---|---------------|----------------|-----------------|
| Respiratory failure                             |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 4 / 21 (19.05%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 8           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 1 / 3           |
| Psychiatric disorders                           |               |                |                 |
| Depression                                      |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Mania   |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Investigations                                  |               |                |                 |
| Alanine aminotransferase increased              |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Aspartate aminotransferase increased            |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Electrocardiogram QT prolonged                  |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Weight decreased                                |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Injury, poisoning and procedural complications  |               |                |                 |
| Laceration                                      |               |                |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rib fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bradycardia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rhythm idioventricular                          |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular extrasystoles                       |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Presyncope                                      |                |                |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |

|   |               |                |                 |
|---|---------------|----------------|-----------------|
| Anaemia   |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Febrile neutropenia                             |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 3 / 8 (37.50%) | 4 / 21 (19.05%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 6          | 6 / 8           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Neutropenia                                     |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Thrombocytopenia                                |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| 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                      |               |                |                 |
| Diarrhoea                                       |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Haematemesis                                    |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Intestinal perforation                          |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Nausea  |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 4 / 4           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Pneumatosis intestinalis                        |               |                |                 |

|   |               |               |                |
|---|---------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Vomiting  |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Skin and subcutaneous tissue disorders          |               |               |                |
| Drug eruption                                   |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Renal and urinary disorders                     |               |               |                |
| Anuria  |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Oliguria  |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Renal failure                                   |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Renal impairment                                |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Endocrine disorders                             |               |               |                |
| Adrenal suppression                             |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Musculoskeletal and connective tissue disorders |                |               |                |
| Osteolysis                                      |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Infections and infestations                     |                |               |                |
| Bacterial infection                             |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Cellulitis                                      |                |               |                |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Escherichia sepsis                              |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| 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 candidiasis                    |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| H1N1 influenza                                  |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Hepatitis B                                     |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Influenza                                       |                |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |

|   |               |                |                 |
|---|---------------|----------------|-----------------|
| Listeria sepsis                                 |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Lower respiratory tract infection               |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Lower respiratory tract infection fungal        |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Pneumococcal infection                          |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Pneumonia                                       |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Respiratory tract infection                     |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 3 / 21 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 8          | 4 / 6           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Sepsis syndrome                                 |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Septic embolus                                  |               |                |                 |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Septic shock                                    |               |                |                 |



|   |               |               |                |
|---|---------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Staphylococcal infection                        |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Tooth infection                                 |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Metabolism and nutrition disorders              |               |               |                |
| Dehydration                                     |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hyperglycaemia                                  |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hypokalaemia                                    |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hyponatraemia                                   |               |               |                |
| subjects affected / exposed                     | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |

|   |                |  |  |
|---|----------------|--|--|
| <b>Serious adverse events</b>                     | PAN 25 mg      |  |  |
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 7 / 9 (77.78%) |  |  |
| number of deaths (all causes)                     | 1              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |  |  |
| Metastases to soft tissue   |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Squamous cell carcinoma   |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Vascular disorders  |                |  |  |
| Deep vein thrombosis  |                |  |  |
| subjects affected / exposed   | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all                     | 2 / 2          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Orthostatic hypotension   |                |  |  |
| subjects affected / exposed   | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all                     | 2 / 2          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Phlebitis   |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Thrombophlebitis superficial  |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| General disorders and administration site conditions                |                |  |  |
| Asthenia  |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Fatigue   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| General physical health deterioration           |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Multiple organ dysfunction syndrome             |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Non-cardiac chest pain                          |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyrexia   |                |  |  |
| subjects affected / exposed                     | 4 / 9 (44.44%) |  |  |
| occurrences causally related to treatment / all | 4 / 10         |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Aspiration                                      |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cough   |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea exertional                             |                |  |  |

|   |               |  |  |
|---|---------------|--|--|
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Pulmonary embolism                              |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Pulmonary haemorrhage                           |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Respiratory failure                             |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Psychiatric disorders                           |               |  |  |
| Depression                                      |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Mania   |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Investigations                                  |               |  |  |
| Alanine aminotransferase increased              |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |
| Aspartate aminotransferase increased            |               |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         |  |  |
| deaths causally related to treatment / all      | 0 / 0         |  |  |

|  |                                 |  |  |
|--|---------------------------------|--|--|
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all               | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Injury, poisoning and procedural<br>complications  |                                 |  |  |
| Laceration<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                     | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Rib fracture<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                   | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Cardiac disorders  |                                 |  |  |
| Acute myocardial infarction<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all    | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all            | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Bradycardia<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                    | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Rhythm idioventricular<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all         | 0 / 9 (0.00%)<br>0 / 0<br>0 / 0 |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Ventricular extrasystoles                       |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Presyncope                                      |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Anaemia   |                |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |
| occurrences causally related to treatment / all | 6 / 8          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Febrile neutropenia                             |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neutropenia                                     |                |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |
| occurrences causally related to treatment / all | 2 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thrombocytopenia                                |                |  |  |
| subjects affected / exposed                     | 3 / 9 (33.33%) |  |  |
| occurrences causally related to treatment / all | 2 / 6          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 3 / 9 (33.33%) |  |  |
| occurrences causally related to treatment / all | 6 / 8          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haematemesis                                    |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Intestinal perforation                          |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumatosis intestinalis                        |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Drug eruption                                   |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Anuria  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oliguria  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal failure                                   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal impairment                                |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Endocrine disorders                             |                |  |  |
| Adrenal suppression                             |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Osteolysis                                      |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bacterial infection                             |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cellulitis                                      |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Escherichia sepsis                              |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal candidiasis                    |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |



|   |                |  |  |  |
|---|----------------|--|--|--|
| H1N1 influenza                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Hepatitis B                                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Influenza                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Listeria sepsis                                 |                |  |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower respiratory tract infection fungal        |                |  |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumococcal infection                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 4          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Respiratory tract infection                     |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sepsis syndrome                                 |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic embolus                                  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 2 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Staphylococcal infection                        |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tooth infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperglycaemia                                  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypokalaemia                                    |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyponatraemia                                   |                |  |  |
| subjects affected / exposed                     | 0 / 9 (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>                                   | PAN 5 mg        | PAN 10 mg       | PAN 20 mg         |
|---|-----------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events               |                 |                 |                   |
| subjects affected / exposed   | 8 / 8 (100.00%) | 8 / 8 (100.00%) | 21 / 21 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                   |
| Cancer pain   |                 |                 |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)   | 1 / 8 (12.50%)  | 0 / 21 (0.00%)    |
| occurrences (all)   | 0               | 2               | 0                 |
| Vascular disorders  |                 |                 |                   |
| Deep vein thrombosis  |                 |                 |                   |
| subjects affected / exposed   | 1 / 8 (12.50%)  | 0 / 8 (0.00%)   | 0 / 21 (0.00%)    |
| occurrences (all)   | 2               | 0               | 0                 |
| Haematoma   |                 |                 |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)   | 1 / 8 (12.50%)  | 0 / 21 (0.00%)    |
| occurrences (all)   | 0               | 2               | 0                 |
| Hot flush   |                 |                 |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)   | 1 / 8 (12.50%)  | 0 / 21 (0.00%)    |
| occurrences (all)   | 0               | 2               | 0                 |
| Hypotension   |                 |                 |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)   | 1 / 8 (12.50%)  | 2 / 21 (9.52%)    |
| occurrences (all)   | 0               | 2               | 4                 |
| Orthostatic hypotension   |                 |                 |                   |
| subjects affected / exposed   | 0 / 8 (0.00%)   | 0 / 8 (0.00%)   | 3 / 21 (14.29%)   |
| occurrences (all)   | 0               | 0               | 6                 |
| Phlebitis   |                 |                 |                   |

|   |                     |                    |                     |
|---|---------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 1 / 8 (12.50%)<br>2 | 0 / 8 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0 |
| General disorders and administration<br>site conditions |                     |                    |                     |
| Asthenia  |                     |                    |                     |
| subjects affected / exposed                             | 1 / 8 (12.50%)      | 3 / 8 (37.50%)     | 7 / 21 (33.33%)     |
| occurrences (all)                                       | 2                   | 6                  | 26                  |
| Chest discomfort  |                     |                    |                     |
| subjects affected / exposed                             | 1 / 8 (12.50%)      | 1 / 8 (12.50%)     | 0 / 21 (0.00%)      |
| occurrences (all)                                       | 2                   | 4                  | 0                   |
| Chills  |                     |                    |                     |
| subjects affected / exposed                             | 2 / 8 (25.00%)      | 0 / 8 (0.00%)      | 1 / 21 (4.76%)      |
| occurrences (all)                                       | 4                   | 0                  | 2                   |
| Discomfort  |                     |                    |                     |
| subjects affected / exposed                             | 0 / 8 (0.00%)       | 1 / 8 (12.50%)     | 0 / 21 (0.00%)      |
| occurrences (all)                                       | 0                   | 2                  | 0                   |
| Fatigue   |                     |                    |                     |
| subjects affected / exposed                             | 6 / 8 (75.00%)      | 3 / 8 (37.50%)     | 7 / 21 (33.33%)     |
| occurrences (all)                                       | 14                  | 8                  | 14                  |
| Feeling abnormal  |                     |                    |                     |
| subjects affected / exposed                             | 1 / 8 (12.50%)      | 0 / 8 (0.00%)      | 0 / 21 (0.00%)      |
| occurrences (all)                                       | 2                   | 0                  | 0                   |
| Influenza like illness                                  |                     |                    |                     |
| subjects affected / exposed                             | 0 / 8 (0.00%)       | 1 / 8 (12.50%)     | 0 / 21 (0.00%)      |
| occurrences (all)                                       | 0                   | 2                  | 0                   |
| Malaise   |                     |                    |                     |
| subjects affected / exposed                             | 1 / 8 (12.50%)      | 0 / 8 (0.00%)      | 1 / 21 (4.76%)      |
| occurrences (all)                                       | 2                   | 0                  | 4                   |
| Non-cardiac chest pain                                  |                     |                    |                     |
| subjects affected / exposed                             | 1 / 8 (12.50%)      | 0 / 8 (0.00%)      | 0 / 21 (0.00%)      |
| occurrences (all)                                       | 2                   | 0                  | 0                   |
| Oedema peripheral                                       |                     |                    |                     |
| subjects affected / exposed                             | 0 / 8 (0.00%)       | 2 / 8 (25.00%)     | 4 / 21 (19.05%)     |
| occurrences (all)                                       | 0                   | 4                  | 12                  |
| Pyrexia   |                     |                    |                     |

|   |                      |                     |                       |
|---|----------------------|---------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)  | 5 / 8 (62.50%)<br>10 | 2 / 8 (25.00%)<br>8 | 7 / 21 (33.33%)<br>30 |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)               | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0  | 1 / 21 (4.76%)<br>2   |
| Reproductive system and breast disorders<br>Prostatitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0   |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0   | 1 / 8 (12.50%)<br>2 | 0 / 21 (0.00%)<br>0   |
| Bronchial obstruction<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0   |
| Catarrh<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0  | 2 / 21 (9.52%)<br>12  |
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 1 / 8 (12.50%)<br>4  | 1 / 8 (12.50%)<br>2 | 3 / 21 (14.29%)<br>6  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0   |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 3 / 8 (37.50%)<br>6  | 0 / 8 (0.00%)<br>0  | 1 / 21 (4.76%)<br>2   |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 8 (0.00%)<br>0   | 1 / 8 (12.50%)<br>2 | 2 / 21 (9.52%)<br>4   |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0   | 1 / 8 (12.50%)<br>2 | 3 / 21 (14.29%)<br>6  |
| Hiccups   |                      |                     |                       |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0               |
| Oropharyngeal pain          |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 4              | 0              | 0               |
| Pleuritic pain              |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Productive cough            |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)           | 4              | 2              | 0               |
| Respiratory depression      |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Rhinorrhoea                 |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)           | 0              | 2              | 2               |
| Psychiatric disorders       |                |                |                 |
| Agitation                   |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)           | 0              | 2              | 2               |
| Anxiety                     |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)           | 0              | 0              | 4               |
| Depressed mood              |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Depression                  |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)           | 0              | 2              | 2               |
| Insomnia                    |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 7 / 21 (33.33%) |
| occurrences (all)           | 2              | 2              | 14              |
| Libido decreased            |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0               |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Mania  |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)                              | 0              | 2              | 0               |
| Mood altered                                   |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences (all)                              | 0              | 0              | 2               |
| Stress   |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0               |
| Investigations                                 |                |                |                 |
| Alanine aminotransferase increased             |                |                |                 |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)                              | 2              | 0              | 4               |
| Aspartate aminotransferase increased           |                |                |                 |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)                              | 2              | 0              | 8               |
| Ejection fraction decreased                    |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)                              | 0              | 2              | 0               |
| Electrocardiogram QT prolonged                 |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)                              | 0              | 4              | 0               |
| Gamma-glutamyltransferase increased            |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 3 / 21 (14.29%) |
| occurrences (all)                              | 0              | 0              | 6               |
| Oxygen saturation decreased                    |                |                |                 |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)                              | 0              | 2              | 0               |
| Weight decreased                               |                |                |                 |
| subjects affected / exposed                    | 2 / 8 (25.00%) | 3 / 8 (37.50%) | 5 / 21 (23.81%) |
| occurrences (all)                              | 6              | 6              | 10              |
| Injury, poisoning and procedural complications |                |                |                 |
| Contusion                                      |                |                |                 |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)                              | 4              | 2              | 0               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Excoriation                 |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Fall                        |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%) |
| occurrences (all)           | 0              | 0              | 2              |
| Femur fracture              |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Foreign body in eye         |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Pelvic fracture             |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Cardiac disorders           |                |                |                |
| Atrial fibrillation         |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 0 / 21 (0.00%) |
| occurrences (all)           | 6              | 2              | 0              |
| Cardiotoxicity              |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%) |
| occurrences (all)           | 0              | 2              | 2              |
| Coronary artery disease     |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Palpitations                |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 2 / 21 (9.52%) |
| occurrences (all)           | 0              | 0              | 4              |
| Tachycardia                 |                |                |                |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Nervous system disorders    |                |                |                |
| Ageusia                     |                |                |                |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%) |
| occurrences (all)           | 0              | 2              | 2              |
| Coordination abnormal       |                |                |                |



|                               |                |                |                 |
|-------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0               |
| Dizziness                     |                |                |                 |
| subjects affected / exposed   | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 5 / 21 (23.81%) |
| occurrences (all)             | 2              | 2              | 18              |
| Dizziness postural            |                |                |                 |
| subjects affected / exposed   | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)             | 2              | 2              | 2               |
| Dysgeusia                     |                |                |                 |
| subjects affected / exposed   | 1 / 8 (12.50%) | 2 / 8 (25.00%) | 3 / 21 (14.29%) |
| occurrences (all)             | 2              | 4              | 6               |
| Essential tremor              |                |                |                 |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)             | 0              | 2              | 0               |
| Head discomfort               |                |                |                 |
| subjects affected / exposed   | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 2              | 0              | 0               |
| Headache                      |                |                |                 |
| subjects affected / exposed   | 2 / 8 (25.00%) | 2 / 8 (25.00%) | 3 / 21 (14.29%) |
| occurrences (all)             | 6              | 4              | 8               |
| Loss of consciousness         |                |                |                 |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)             | 0              | 2              | 2               |
| Neuralgia                     |                |                |                 |
| subjects affected / exposed   | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 2              | 0              | 0               |
| Neuropathy peripheral         |                |                |                 |
| subjects affected / exposed   | 3 / 8 (37.50%) | 1 / 8 (12.50%) | 2 / 21 (9.52%)  |
| occurrences (all)             | 6              | 2              | 4               |
| Paraesthesia                  |                |                |                 |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 0              | 0              | 0               |
| Peripheral sensory neuropathy |                |                |                 |
| subjects affected / exposed   | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)             | 0              | 2              | 2               |
| Sciatica                      |                |                |                 |

|                                      |                |                |                  |
|--------------------------------------|----------------|----------------|------------------|
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                    | 2              | 0              | 0                |
| Somnolence                           |                |                |                  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                    | 2              | 0              | 0                |
| Syncope                              |                |                |                  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences (all)                    | 2              | 0              | 2                |
| Tremor                               |                |                |                  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)                    | 2              | 2              | 0                |
| Blood and lymphatic system disorders |                |                |                  |
| Anaemia                              |                |                |                  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 3 / 8 (37.50%) | 13 / 21 (61.90%) |
| occurrences (all)                    | 10             | 18             | 126              |
| Febrile neutropenia                  |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 2 / 21 (9.52%)   |
| occurrences (all)                    | 0              | 2              | 4                |
| Leukopenia                           |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 3 / 21 (14.29%)  |
| occurrences (all)                    | 0              | 2              | 14               |
| Lymphopenia                          |                |                |                  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences (all)                    | 2              | 0              | 2                |
| Neutropenia                          |                |                |                  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 4 / 8 (50.00%) | 13 / 21 (61.90%) |
| occurrences (all)                    | 14             | 30             | 256              |
| Thrombocytopenia                     |                |                |                  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 3 / 8 (37.50%) | 13 / 21 (61.90%) |
| occurrences (all)                    | 4              | 16             | 162              |
| Ear and labyrinth disorders          |                |                |                  |
| Vertigo                              |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Eye disorders                        |                |                |                  |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| Cataract                    |                |                |                  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)           | 4              | 0              | 0                |
| Conjunctival haemorrhage    |                |                |                  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences (all)           | 0              | 0              | 4                |
| Vision blurred              |                |                |                  |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)           | 2              | 2              | 0                |
| Vitreous floaters           |                |                |                  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)           | 2              | 0              | 0                |
| Gastrointestinal disorders  |                |                |                  |
| Abdominal pain              |                |                |                  |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 8 (25.00%) | 2 / 21 (9.52%)   |
| occurrences (all)           | 2              | 4              | 6                |
| Abdominal pain upper        |                |                |                  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 2 / 21 (9.52%)   |
| occurrences (all)           | 0              | 0              | 8                |
| Aphthous ulcer              |                |                |                  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)           | 0              | 2              | 0                |
| Constipation                |                |                |                  |
| subjects affected / exposed | 4 / 8 (50.00%) | 1 / 8 (12.50%) | 10 / 21 (47.62%) |
| occurrences (all)           | 8              | 2              | 24               |
| Diarrhoea                   |                |                |                  |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 8 (37.50%) | 13 / 21 (61.90%) |
| occurrences (all)           | 12             | 12             | 66               |
| Dry mouth                   |                |                |                  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)           | 0              | 2              | 0                |
| Dyspepsia                   |                |                |                  |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 1 / 21 (4.76%)   |
| occurrences (all)           | 2              | 2              | 2                |
| Dysphagia                   |                |                |                  |

|                                  |                |                |                  |
|----------------------------------|----------------|----------------|------------------|
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences (all)                | 0              | 0              | 2                |
| Flatulence                       |                |                |                  |
| subjects affected / exposed      | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 1 / 21 (4.76%)   |
| occurrences (all)                | 2              | 2              | 2                |
| Gastrooesophageal reflux disease |                |                |                  |
| subjects affected / exposed      | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 2 / 21 (9.52%)   |
| occurrences (all)                | 2              | 0              | 4                |
| Gingival bleeding                |                |                |                  |
| subjects affected / exposed      | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                | 2              | 0              | 0                |
| Mouth ulceration                 |                |                |                  |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)   |
| occurrences (all)                | 0              | 2              | 6                |
| Nausea                           |                |                |                  |
| subjects affected / exposed      | 2 / 8 (25.00%) | 4 / 8 (50.00%) | 11 / 21 (52.38%) |
| occurrences (all)                | 4              | 8              | 28               |
| Oesophagitis                     |                |                |                  |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)   |
| occurrences (all)                | 0              | 2              | 2                |
| Oral pain                        |                |                |                  |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)   |
| occurrences (all)                | 0              | 0              | 2                |
| Retching                         |                |                |                  |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)                | 0              | 2              | 0                |
| Stomatitis                       |                |                |                  |
| subjects affected / exposed      | 1 / 8 (12.50%) | 2 / 8 (25.00%) | 1 / 21 (4.76%)   |
| occurrences (all)                | 2              | 4              | 2                |
| Tooth disorder                   |                |                |                  |
| subjects affected / exposed      | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                | 2              | 0              | 0                |
| Toothache                        |                |                |                  |
| subjects affected / exposed      | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)   |
| occurrences (all)                | 0              | 2              | 2                |
| Vomiting                         |                |                |                  |

|  |                    |                     |                       |
|--|--------------------|---------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0 | 1 / 8 (12.50%)<br>2 | 6 / 21 (28.57%)<br>20 |
| Hepatobiliary disorders                          |                    |                     |                       |
| Hepatotoxicity                                   |                    |                     |                       |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 1 / 8 (12.50%)      | 1 / 21 (4.76%)        |
| occurrences (all)                                | 0                  | 2                   | 2                     |
| Hyperbilirubinaemia                              |                    |                     |                       |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 8 (0.00%)       | 2 / 21 (9.52%)        |
| occurrences (all)                                | 0                  | 0                   | 6                     |
| Skin and subcutaneous tissue disorders           |                    |                     |                       |
| Alopecia   |                    |                     |                       |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 8 (0.00%)       | 0 / 21 (0.00%)        |
| occurrences (all)                                | 0                  | 0                   | 0                     |
| Dermal cyst                                      |                    |                     |                       |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 0 / 8 (0.00%)       | 0 / 21 (0.00%)        |
| occurrences (all)                                | 2                  | 0                   | 0                     |
| Dry skin   |                    |                     |                       |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 1 / 8 (12.50%)      | 0 / 21 (0.00%)        |
| occurrences (all)                                | 2                  | 2                   | 0                     |
| Erythema   |                    |                     |                       |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 8 (0.00%)       | 1 / 21 (4.76%)        |
| occurrences (all)                                | 0                  | 0                   | 2                     |
| Hyperhidrosis                                    |                    |                     |                       |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 1 / 8 (12.50%)      | 0 / 21 (0.00%)        |
| occurrences (all)                                | 2                  | 2                   | 0                     |
| Ingrowing nail                                   |                    |                     |                       |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 0 / 8 (0.00%)       | 0 / 21 (0.00%)        |
| occurrences (all)                                | 2                  | 0                   | 0                     |
| Precancerous skin lesion                         |                    |                     |                       |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 0 / 8 (0.00%)       | 0 / 21 (0.00%)        |
| occurrences (all)                                | 2                  | 0                   | 0                     |
| Pruritus   |                    |                     |                       |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 0 / 8 (0.00%)       | 1 / 21 (4.76%)        |
| occurrences (all)                                | 2                  | 0                   | 2                     |
| Rash   |                    |                     |                       |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                | 3 / 8 (37.50%)<br>6 | 2 / 8 (25.00%)<br>6 | 2 / 21 (9.52%)<br>4 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 8 (12.50%)<br>2 | 0 / 8 (0.00%)<br>0  | 1 / 21 (4.76%)<br>4 |
| Renal and urinary disorders   |                     |                     |                     |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>2 | 0 / 21 (0.00%)<br>0 |
| Micturition disorder<br>subjects affected / exposed<br>occurrences (all)        | 1 / 8 (12.50%)<br>2 | 0 / 8 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>2 | 0 / 21 (0.00%)<br>0 |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 8 (25.00%)<br>4 | 1 / 8 (12.50%)<br>2 | 0 / 21 (0.00%)<br>0 |
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)            | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |
| Endocrine disorders   |                     |                     |                     |
| Adrenal insufficiency<br>subjects affected / exposed<br>occurrences (all)       | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)              | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>2 | 1 / 21 (4.76%)<br>2 |
| Steroid withdrawal syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>2 | 0 / 21 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders                                 |                     |                     |                     |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 2 / 21 (9.52%)<br>6 |
| Back pain   |                     |                     |                     |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 8 (37.50%) | 1 / 8 (12.50%) | 3 / 21 (14.29%) |
| occurrences (all)           | 8              | 2              | 10              |
| Bone pain                   |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Joint swelling              |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Muscle spasms               |                |                |                 |
| subjects affected / exposed | 6 / 8 (75.00%) | 2 / 8 (25.00%) | 3 / 21 (14.29%) |
| occurrences (all)           | 20             | 4              | 6               |
| Muscular weakness           |                |                |                 |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 8 (25.00%) | 2 / 21 (9.52%)  |
| occurrences (all)           | 6              | 4              | 4               |
| Musculoskeletal chest pain  |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0               |
| Osteoarthritis              |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 3 / 8 (37.50%) | 1 / 8 (12.50%) | 2 / 21 (9.52%)  |
| occurrences (all)           | 6              | 2              | 6               |
| Infections and infestations |                |                |                 |
| Campylobacter infection     |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Gastroenteritis             |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 1 / 21 (4.76%)  |
| occurrences (all)           | 0              | 2              | 2               |
| Laryngitis                  |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Localised infection         |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences (all)           | 2              | 0              | 2               |

|   |                      |                      |                       |
|---|----------------------|----------------------|-----------------------|
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>4  | 1 / 8 (12.50%)<br>4  | 1 / 21 (4.76%)<br>2   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 2 / 21 (9.52%)<br>4   |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0   | 1 / 8 (12.50%)<br>4  | 1 / 21 (4.76%)<br>2   |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 8 (12.50%)<br>2  | 0 / 8 (0.00%)<br>0   | 1 / 21 (4.76%)<br>2   |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 0 / 8 (0.00%)<br>0   | 1 / 8 (12.50%)<br>8  | 3 / 21 (14.29%)<br>10 |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   |
| Subcutaneous abscess<br>subjects affected / exposed<br>occurrences (all)              | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 8 (50.00%)<br>28 | 2 / 8 (25.00%)<br>28 | 4 / 21 (19.05%)<br>8  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 0 / 8 (0.00%)<br>0   | 0 / 8 (0.00%)<br>0   | 2 / 21 (9.52%)<br>4   |



|                                      |                |                |                  |
|--------------------------------------|----------------|----------------|------------------|
| Vulvitis                             |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Metabolism and nutrition disorders   |                |                |                  |
| Decreased appetite                   |                |                |                  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 2 / 8 (25.00%) | 5 / 21 (23.81%)  |
| occurrences (all)                    | 6              | 4              | 18               |
| Dehydration                          |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 2 / 21 (9.52%)   |
| occurrences (all)                    | 0              | 0              | 4                |
| Diabetes mellitus inadequate control |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 0 / 21 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Hyperglycaemia                       |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 3 / 8 (37.50%) | 7 / 21 (33.33%)  |
| occurrences (all)                    | 0              | 12             | 24               |
| Hypermagnesaemia                     |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)                    | 0              | 2              | 0                |
| Hypertriglyceridaemia                |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 1 / 8 (12.50%) | 0 / 21 (0.00%)   |
| occurrences (all)                    | 0              | 2              | 0                |
| Hypoalbuminaemia                     |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 2 / 21 (9.52%)   |
| occurrences (all)                    | 0              | 0              | 4                |
| Hypocalcaemia                        |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 2 / 8 (25.00%) | 7 / 21 (33.33%)  |
| occurrences (all)                    | 0              | 12             | 30               |
| Hypokalaemia                         |                |                |                  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 5 / 8 (62.50%) | 10 / 21 (47.62%) |
| occurrences (all)                    | 6              | 24             | 38               |
| Hypomagnesaemia                      |                |                |                  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 2 / 8 (25.00%) | 3 / 21 (14.29%)  |
| occurrences (all)                    | 0              | 14             | 10               |
| Hyponatraemia                        |                |                |                  |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 8 (0.00%)  | 3 / 21 (14.29%) |
| occurrences (all)           | 6              | 0              | 8               |
| Hypophosphataemia           |                |                |                 |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | 4 / 21 (19.05%) |
| occurrences (all)           | 2              | 4              | 8               |
| Hypoproteinaemia            |                |                |                 |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 8 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences (all)           | 0              | 0              | 2               |

|   |                 |  |  |
|---|-----------------|--|--|
| <b>Non-serious adverse events</b>                                   | PAN 25 mg       |  |  |
| Total subjects affected by non-serious adverse events               |                 |  |  |
| subjects affected / exposed   | 9 / 9 (100.00%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |  |  |
| Cancer pain   |                 |  |  |
| subjects affected / exposed   | 1 / 9 (11.11%)  |  |  |
| occurrences (all)   | 2               |  |  |
| Vascular disorders  |                 |  |  |
| Deep vein thrombosis  |                 |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)   |  |  |
| occurrences (all)   | 0               |  |  |
| Haematoma   |                 |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)   |  |  |
| occurrences (all)   | 0               |  |  |
| Hot flush   |                 |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)   |  |  |
| occurrences (all)   | 0               |  |  |
| Hypotension   |                 |  |  |
| subjects affected / exposed   | 1 / 9 (11.11%)  |  |  |
| occurrences (all)   | 4               |  |  |
| Orthostatic hypotension   |                 |  |  |
| subjects affected / exposed   | 3 / 9 (33.33%)  |  |  |
| occurrences (all)   | 12              |  |  |
| Phlebitis   |                 |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)   |  |  |
| occurrences (all)   | 0               |  |  |
| General disorders and administration site conditions                |                 |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| Asthenia                    |                |  |  |
| subjects affected / exposed | 6 / 9 (66.67%) |  |  |
| occurrences (all)           | 20             |  |  |
| Chest discomfort            |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Chills                      |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Discomfort                  |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Fatigue                     |                |  |  |
| subjects affected / exposed | 2 / 9 (22.22%) |  |  |
| occurrences (all)           | 12             |  |  |
| Feeling abnormal            |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Influenza like illness      |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Malaise                     |                |  |  |
| subjects affected / exposed | 2 / 9 (22.22%) |  |  |
| occurrences (all)           | 4              |  |  |
| Non-cardiac chest pain      |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Oedema peripheral           |                |  |  |
| subjects affected / exposed | 5 / 9 (55.56%) |  |  |
| occurrences (all)           | 10             |  |  |
| Pyrexia                     |                |  |  |
| subjects affected / exposed | 2 / 9 (22.22%) |  |  |
| occurrences (all)           | 10             |  |  |
| Immune system disorders     |                |  |  |
| Seasonal allergy            |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Reproductive system and breast disorders        |                |  |  |
| Prostatitis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Asthma  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Bronchial obstruction                           |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Catarrh   |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Cough   |                |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Dysphonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Dyspnoea exertional                             |                |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Epistaxis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Hiccups   |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Oropharyngeal pain                              |                |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 9 (22.22%) |  |  |
| occurrences (all)           | 4              |  |  |
| Pleuritic pain              |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Productive cough            |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Respiratory depression      |                |  |  |
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 2              |  |  |
| Rhinorrhoea                 |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Psychiatric disorders       |                |  |  |
| Agitation                   |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Anxiety                     |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Depressed mood              |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Depression                  |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Insomnia                    |                |  |  |
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 2              |  |  |
| Libido decreased            |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Mania                       |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Mood altered<br>subjects affected / exposed<br>occurrences (all)  | 1 / 9 (11.11%)<br>4 |  |  |
| Stress<br>subjects affected / exposed<br>occurrences (all)  | 1 / 9 (11.11%)<br>2 |  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)        | 1 / 9 (11.11%)<br>2 |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 9 (0.00%)<br>0  |  |  |
| Ejection fraction decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 9 (0.00%)<br>0  |  |  |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 9 (0.00%)<br>0  |  |  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 9 (11.11%)<br>2 |  |  |
| Oxygen saturation decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 9 (0.00%)<br>0  |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 9 (11.11%)<br>2 |  |  |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>2 |  |  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)   | 0 / 9 (0.00%)<br>0  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| Fall                        |                |  |  |
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 2              |  |  |
| Femur fracture              |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Foreign body in eye         |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Pelvic fracture             |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Cardiac disorders           |                |  |  |
| Atrial fibrillation         |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Cardiotoxicity              |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Coronary artery disease     |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Palpitations                |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Tachycardia                 |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Nervous system disorders    |                |  |  |
| Ageusia                     |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Coordination abnormal       |                |  |  |
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 2              |  |  |
| Dizziness                   |                |  |  |

|                               |                |  |  |
|-------------------------------|----------------|--|--|
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Dizziness postural            |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Dysgeusia                     |                |  |  |
| subjects affected / exposed   | 3 / 9 (33.33%) |  |  |
| occurrences (all)             | 6              |  |  |
| Essential tremor              |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Head discomfort               |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Headache                      |                |  |  |
| subjects affected / exposed   | 2 / 9 (22.22%) |  |  |
| occurrences (all)             | 4              |  |  |
| Loss of consciousness         |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Neuralgia                     |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Neuropathy peripheral         |                |  |  |
| subjects affected / exposed   | 1 / 9 (11.11%) |  |  |
| occurrences (all)             | 2              |  |  |
| Paraesthesia                  |                |  |  |
| subjects affected / exposed   | 1 / 9 (11.11%) |  |  |
| occurrences (all)             | 2              |  |  |
| Peripheral sensory neuropathy |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Sciatica                      |                |  |  |
| subjects affected / exposed   | 0 / 9 (0.00%)  |  |  |
| occurrences (all)             | 0              |  |  |
| Somnolence                    |                |  |  |



|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Syncope</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tremor</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 9 (11.11%)</p> <p>2</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p>   |  |  |
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Febrile neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 9 (66.67%)</p> <p>36</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>4 / 9 (44.44%)</p> <p>26</p> <p>1 / 9 (11.11%)</p> <p>4</p> <p>8 / 9 (88.89%)</p> <p>58</p> <p>8 / 9 (88.89%)</p> <p>52</p> |  |  |
| <p>Ear and labyrinth disorders</p> <p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 9 (11.11%)</p> <p>2</p>   |  |  |
| <p>Eye disorders</p> <p>Cataract</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Conjunctival haemorrhage</p>  | <p>0 / 9 (0.00%)</p> <p>0</p>  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 4              |  |  |
| Vision blurred              |                |  |  |
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 2              |  |  |
| Vitreous floaters           |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Gastrointestinal disorders  |                |  |  |
| Abdominal pain              |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Abdominal pain upper        |                |  |  |
| subjects affected / exposed | 2 / 9 (22.22%) |  |  |
| occurrences (all)           | 4              |  |  |
| Aphthous ulcer              |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Constipation                |                |  |  |
| subjects affected / exposed | 3 / 9 (33.33%) |  |  |
| occurrences (all)           | 6              |  |  |
| Diarrhoea                   |                |  |  |
| subjects affected / exposed | 6 / 9 (66.67%) |  |  |
| occurrences (all)           | 36             |  |  |
| Dry mouth                   |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Dyspepsia                   |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |
| Dysphagia                   |                |  |  |
| subjects affected / exposed | 1 / 9 (11.11%) |  |  |
| occurrences (all)           | 2              |  |  |
| Flatulence                  |                |  |  |
| subjects affected / exposed | 0 / 9 (0.00%)  |  |  |
| occurrences (all)           | 0              |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0   |  |  |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)                | 0 / 9 (0.00%)<br>0   |  |  |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 9 (0.00%)<br>0   |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | 5 / 9 (55.56%)<br>12 |  |  |
| Oesophagitis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 9 (0.00%)<br>0   |  |  |
| Oral pain<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 9 (11.11%)<br>2  |  |  |
| Retching<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 9 (0.00%)<br>0   |  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 9 (0.00%)<br>0   |  |  |
| Tooth disorder<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 9 (0.00%)<br>0   |  |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 9 (0.00%)<br>0   |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 9 (11.11%)<br>4  |  |  |
| Hepatobiliary disorders<br>Hepatotoxicity  |                      |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed            | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Hyperbilirubinaemia                    |                |  |  |
| subjects affected / exposed            | 1 / 9 (11.11%) |  |  |
| occurrences (all)                      | 8              |  |  |
| Skin and subcutaneous tissue disorders |                |  |  |
| Alopecia                               |                |  |  |
| subjects affected / exposed            | 1 / 9 (11.11%) |  |  |
| occurrences (all)                      | 2              |  |  |
| Dermal cyst                            |                |  |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Dry skin                               |                |  |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Erythema                               |                |  |  |
| subjects affected / exposed            | 1 / 9 (11.11%) |  |  |
| occurrences (all)                      | 2              |  |  |
| Hyperhidrosis                          |                |  |  |
| subjects affected / exposed            | 1 / 9 (11.11%) |  |  |
| occurrences (all)                      | 2              |  |  |
| Ingrowing nail                         |                |  |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Precancerous skin lesion               |                |  |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |
| Pruritus                               |                |  |  |
| subjects affected / exposed            | 1 / 9 (11.11%) |  |  |
| occurrences (all)                      | 2              |  |  |
| Rash                                   |                |  |  |
| subjects affected / exposed            | 2 / 9 (22.22%) |  |  |
| occurrences (all)                      | 4              |  |  |
| Urticaria                              |                |  |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                      | 0              |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Renal and urinary disorders                     |                |  |  |
| Dysuria   |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Micturition disorder                            |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Nephrolithiasis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Pollakiuria                                     |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Renal impairment                                |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Endocrine disorders                             |                |  |  |
| Adrenal insufficiency                           |                |  |  |
| subjects affected / exposed                     | 1 / 9 (11.11%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Hypothyroidism                                  |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Steroid withdrawal syndrome                     |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Back pain                                       |                |  |  |
| subjects affected / exposed                     | 2 / 9 (22.22%) |  |  |
| occurrences (all)                               | 6              |  |  |
| Bone pain                                       |                |  |  |
| subjects affected / exposed                     | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                               | 0              |  |  |

|                                   |                |  |  |
|-----------------------------------|----------------|--|--|
| Joint swelling                    |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Muscle spasms                     |                |  |  |
| subjects affected / exposed       | 1 / 9 (11.11%) |  |  |
| occurrences (all)                 | 4              |  |  |
| Muscular weakness                 |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Musculoskeletal chest pain        |                |  |  |
| subjects affected / exposed       | 2 / 9 (22.22%) |  |  |
| occurrences (all)                 | 4              |  |  |
| Osteoarthritis                    |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Pain in extremity                 |                |  |  |
| subjects affected / exposed       | 1 / 9 (11.11%) |  |  |
| occurrences (all)                 | 2              |  |  |
| Infections and infestations       |                |  |  |
| Campylobacter infection           |                |  |  |
| subjects affected / exposed       | 1 / 9 (11.11%) |  |  |
| occurrences (all)                 | 4              |  |  |
| Gastroenteritis                   |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Laryngitis                        |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Localised infection               |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Lower respiratory tract infection |                |  |  |
| subjects affected / exposed       | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Nasopharyngitis                   |                |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                  | 0              |  |  |
| Oral herpes                        |                |  |  |
| subjects affected / exposed        | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                  | 0              |  |  |
| Pharyngitis                        |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Pneumonia                          |                |  |  |
| subjects affected / exposed        | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                  | 0              |  |  |
| Respiratory tract infection        |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Sinusitis                          |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Subcutaneous abscess               |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Tonsillitis                        |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Tooth infection                    |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 4              |  |  |
| Upper respiratory tract infection  |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Urinary tract infection            |                |  |  |
| subjects affected / exposed        | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                  | 0              |  |  |
| Vulvitis                           |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Metabolism and nutrition disorders |                |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| Decreased appetite                   |                |  |  |
| subjects affected / exposed          | 6 / 9 (66.67%) |  |  |
| occurrences (all)                    | 14             |  |  |
| Dehydration                          |                |  |  |
| subjects affected / exposed          | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Diabetes mellitus inadequate control |                |  |  |
| subjects affected / exposed          | 1 / 9 (11.11%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Hyperglycaemia                       |                |  |  |
| subjects affected / exposed          | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Hypermagnesaemia                     |                |  |  |
| subjects affected / exposed          | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Hypertriglyceridaemia                |                |  |  |
| subjects affected / exposed          | 0 / 9 (0.00%)  |  |  |
| occurrences (all)                    | 0              |  |  |
| Hypoalbuminaemia                     |                |  |  |
| subjects affected / exposed          | 1 / 9 (11.11%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Hypocalcaemia                        |                |  |  |
| subjects affected / exposed          | 4 / 9 (44.44%) |  |  |
| occurrences (all)                    | 24             |  |  |
| Hypokalaemia                         |                |  |  |
| subjects affected / exposed          | 3 / 9 (33.33%) |  |  |
| occurrences (all)                    | 28             |  |  |
| Hypomagnesaemia                      |                |  |  |
| subjects affected / exposed          | 2 / 9 (22.22%) |  |  |
| occurrences (all)                    | 10             |  |  |
| Hyponatraemia                        |                |  |  |
| subjects affected / exposed          | 1 / 9 (11.11%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Hypophosphataemia                    |                |  |  |
| subjects affected / exposed          | 4 / 9 (44.44%) |  |  |
| occurrences (all)                    | 20             |  |  |



|  |                     |  |  |
|--|---------------------|--|--|
| Hypoproteinaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>2 |  |  |
|--|---------------------|--|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 27 February 2008 | Protocol Amendment 1: Lenalidomide (Revlimid®) is a highly-regulated drug that has been recently approved by only a small number of health authorities around the world. In order for Novartis to use Revlimid® as a combination partner with LBH589 in the CLBH589B2206 trial, the company has entered into a Collaboration Agreement with Celgene Corporation, the manufacturers of Revlimid®. Celgene has agreed to provide Novartis with sufficient supplies of Revlimid® at no cost in exchange for the final study report. However, one of Novartis' key contractual obligations is to allow Celgene to review and comment on the original CLBH589B2206 Protocol Version 00, dated 18 April 2007. Celgene has completed their review, and the primary purpose of this amendment is to incorporate their comments into a new version of the document. In addition, there have been some adjustments made to the Bayesian statistical model being used in the trial. The details of these changes together with the correction of minor inconsistencies are described below. |
| 16 May 2011      | <p>Amendment 2 Summary of changes:</p> <ul style="list-style-type: none"><li>• Reduce the number of visits and assessments for the ongoing patients:<ul style="list-style-type: none"><li>• Reduce from weekly to biweekly the frequency for non labs AE assessments</li><li>• Reduce ECG monitoring schedule frequency following program wide change</li></ul></li><li>• Points updated and / or clarified:<ul style="list-style-type: none"><li>• Clarification on the timing and wording for re-assessment of bone lesions</li><li>• Update of the disease status categories for Investigator's assessment, introducing the category of Minimal Response (MR) in accordance with the update of IMWG response criteria.</li><li>• Add definition for "clinical relapse" criterion.</li><li>• Update the Safety Set definition and define the Fully Analysis set as per updated Novartis standard definitions.</li></ul></li><li>• Update to the safety section of the combination partner drug</li></ul>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Novartis decided to terminate study enrollment on 08 Sep 2010 as there were complex changes in the dosing schedule required from safety perspective after a protocol defined routine review of safety data.

Notes: