



## Clinical trial results:

**A multicenter, randomized, double-blind, placebocontrolled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma**

### Summary

|                          |                                           |
|--------------------------|-------------------------------------------|
| EudraCT number           | 2009-015507-52                            |
| Trial protocol           | SE FI DE NL BE DK IT FR ES CZ PL GB AT GR |
| Global end of trial date | 30 July 2015                              |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 13 August 2016 |
| First version publication date | 13 August 2016 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLBH589D2308 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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 612341111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 612341111, |

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                       | 30 July 2015 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 30 July 2015 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to compare progression-free survival (PFS) in patients treated with panobinostat (PAN) in combination with bortezomib (BTZ)/dexamethasone (Dex) vs. patients treated with placebo (PBO) in combination with bortezomib/dexamethasone. The key secondary objective was to compare overall survival (OS) between treatment arms.

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                          | 21 December 2009 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 28 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Argentina: 9       |
| Country: Number of subjects enrolled | Australia: 14      |
| Country: Number of subjects enrolled | Austria: 8         |
| Country: Number of subjects enrolled | Belgium: 12        |
| Country: Number of subjects enrolled | Brazil: 37         |
| Country: Number of subjects enrolled | Canada: 21         |
| Country: Number of subjects enrolled | China: 45          |
| Country: Number of subjects enrolled | Czech Republic: 13 |
| Country: Number of subjects enrolled | Denmark: 16        |
| Country: Number of subjects enrolled | Egypt: 16          |
| Country: Number of subjects enrolled | Finland: 6         |
| Country: Number of subjects enrolled | France: 24         |
| Country: Number of subjects enrolled | Germany: 63        |
| Country: Number of subjects enrolled | Greece: 17         |
| Country: Number of subjects enrolled | Hong Kong: 6       |
| Country: Number of subjects enrolled | Israel: 5          |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Italy: 45              |
| Country: Number of subjects enrolled | Japan: 34              |
| Country: Number of subjects enrolled | Korea, Republic of: 68 |
| Country: Number of subjects enrolled | Lebanon: 5             |
| Country: Number of subjects enrolled | Mexico: 1              |
| Country: Number of subjects enrolled | Netherlands: 12        |
| Country: Number of subjects enrolled | Norway: 5              |
| Country: Number of subjects enrolled | Poland: 21             |
| Country: Number of subjects enrolled | Russian Federation: 17 |
| Country: Number of subjects enrolled | Singapore: 10          |
| Country: Number of subjects enrolled | South Africa: 7        |
| Country: Number of subjects enrolled | Spain: 38              |
| Country: Number of subjects enrolled | Sweden: 25             |
| Country: Number of subjects enrolled | Taiwan: 18             |
| Country: Number of subjects enrolled | Thailand: 45           |
| Country: Number of subjects enrolled | Turkey: 21             |
| Country: Number of subjects enrolled | United Kingdom: 30     |
| Country: Number of subjects enrolled | United States: 54      |
| Worldwide total number of subjects   | 768                    |
| EEA total number of subjects         | 335                    |

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)                      | 445 |
| From 65 to 84 years                       | 323 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 768 eligible patients were randomized 1:1 to the panobinostat and control arms. Central randomization was stratified 1) by number of prior lines of anti-myeloma therapy: 1 vs. 2 or 3 and 2) by prior use of bortezomib: Yes vs. No.

### Period 1

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

### Arms

|                              |                                           |
|------------------------------|-------------------------------------------|
| Are arms mutually exclusive? | Yes                                       |
| <b>Arm title</b>             | Panobinostat + Bortezomib + Dexamethasone |

Arm description:

Panobinostat was given 20 mg hard gelatin capsules . Bortezomib was given at 1.3 mg/m<sup>2</sup> as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.

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

Dosage and administration details:

Panobinostat was given 20 mg capsules

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Placebo + Bortezomib + Dexamethasone |
|------------------|--------------------------------------|

Arm description:

Placebo was given as a hard gelatin capsule in the image of Panobinostat . Bortezomib was given at 1.3 mg/m<sup>2</sup> as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.

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

Dosage and administration details:

placebo hard capsule match of panobinostat

| <b>Number of subjects in period 1</b> | <b>Panobinostat +<br/>Bortezomib +<br/>Dexamethasone</b> | <b>Placebo +<br/>Bortezomib +<br/>Dexamethasone</b> |
|---------------------------------------|----------------------------------------------------------|-----------------------------------------------------|
| Started                               | 387                                                      | 381                                                 |
| Completed                             | 102                                                      | 102                                                 |
| Not completed                         | 285                                                      | 279                                                 |
| Adverse event, serious fatal          | 21                                                       | 17                                                  |
| Consent withdrawn by subject          | 34                                                       | 18                                                  |
| Disease progression                   | 82                                                       | 153                                                 |
| Adverse event, non-fatal              | 130                                                      | 66                                                  |
| New Cancer therapy                    | 4                                                        | 7                                                   |
| Administrative problems               | 2                                                        | 1                                                   |
| Untreated                             | 5                                                        | 5                                                   |
| Abnormal test procedure results       | 3                                                        | 8                                                   |
| Lost to follow-up                     | 1                                                        | -                                                   |
| Protocol deviation                    | 3                                                        | 4                                                   |

## Baseline characteristics

### Reporting groups

|                       |                                           |
|-----------------------|-------------------------------------------|
| Reporting group title | Panobinostat + Bortezomib + Dexamethasone |
|-----------------------|-------------------------------------------|

Reporting group description:

Panobinostat was given 20 mg hard gelatin capsules . Bortezomib was given at 1.3 mg/m<sup>2</sup> as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Placebo + Bortezomib + Dexamethasone |
|-----------------------|--------------------------------------|

Reporting group description:

Placebo was given as a hard gelatin capsule in the image of Panobinostat . Bortezomib was given at 1.3 mg/m<sup>2</sup> as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.

| Reporting group values                                | Panobinostat +<br>Bortezomib +<br>Dexamethasone | Placebo +<br>Bortezomib +<br>Dexamethasone | Total |
|-------------------------------------------------------|-------------------------------------------------|--------------------------------------------|-------|
| Number of subjects                                    | 387                                             | 381                                        | 768   |
| Age categorical<br>Units: Subjects                    |                                                 |                                            |       |
| In utero                                              | 0                                               | 0                                          | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                               | 0                                          | 0     |
| Newborns (0-27 days)                                  | 0                                               | 0                                          | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                                               | 0                                          | 0     |
| Children (2-11 years)                                 | 0                                               | 0                                          | 0     |
| Adolescents (12-17 years)                             | 0                                               | 0                                          | 0     |
| Adults (18-64 years)                                  | 225                                             | 220                                        | 445   |
| From 65-84 years                                      | 162                                             | 161                                        | 323   |
| 85 years and over                                     | 0                                               | 0                                          | 0     |
| Age Continuous<br>Units: years                        |                                                 |                                            |       |
| arithmetic mean                                       | 62.4                                            | 61.8                                       |       |
| standard deviation                                    | ± 9.34                                          | ± 9.43                                     | -     |
| Gender, Male/Female<br>Units: participants            |                                                 |                                            |       |
| Female                                                | 185                                             | 176                                        | 361   |
| Male                                                  | 202                                             | 205                                        | 407   |
| Race/Ethnicity, Customized<br>Units: Subjects         |                                                 |                                            |       |
| Caucasian                                             | 249                                             | 250                                        | 499   |
| Asian                                                 | 128                                             | 104                                        | 232   |
| Black                                                 | 5                                               | 17                                         | 22    |
| Other                                                 | 5                                               | 10                                         | 15    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                     |                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Reporting group title                                                                                                                                                                                                               | Panobinostat + Bortezomib + Dexamethasone |
| Reporting group description:                                                                                                                                                                                                        |                                           |
| Panobinostat was given 20 mg hard gelatin capsules . Bortezomib was given at 1.3 mg/m <sup>2</sup> as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.                       |                                           |
| Reporting group title                                                                                                                                                                                                               | Placebo + Bortezomib + Dexamethasone      |
| Reporting group description:                                                                                                                                                                                                        |                                           |
| Placebo was given as a hard gelatin capsule in the image of Panobinostat . Bortezomib was given at 1.3 mg/m <sup>2</sup> as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day. |                                           |

### Primary: Progression-free survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

|                        |                                                                                                                                                                                                           |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Progression-free survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. |
| End point description: |                                                                                                                                                                                                           |
| End point type         | Primary                                                                                                                                                                                                   |
| End point timeframe:   |                                                                                                                                                                                                           |
| 45 months              |                                                                                                                                                                                                           |

| End point values            | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|-----------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type          | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed | 387                                       | 381                                  |  |  |
| Units: number of events     | 207                                       | 260                                  |  |  |

### Statistical analyses

|                                         |                                                                                  |
|-----------------------------------------|----------------------------------------------------------------------------------|
| Statistical analysis title              | investigator assessment using mEBMT                                              |
| Comparison groups                       | Panobinostat + Bortezomib + Dexamethasone v Placebo + Bortezomib + Dexamethasone |
| Number of subjects included in analysis | 768                                                                              |
| Analysis specification                  | Pre-specified                                                                    |
| Analysis type                           | superiority                                                                      |
| P-value                                 | < 0.0001                                                                         |
| Method                                  | Logrank                                                                          |
| Parameter estimate                      | Hazard ratio (HR)                                                                |
| Point estimate                          | 0.63                                                                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.52    |
| upper limit         | 0.76    |

**Primary: Progression Free Survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.**

|                 |                                                                                                                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Progression Free Survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

45 months

| End point values                 | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|----------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type               | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed      | 387                                       | 381                                  |  |  |
| Units: months                    |                                           |                                      |  |  |
| median (confidence interval 95%) | 11.99 (10.32 to 12.94)                    | 8.8 (7.56 to 9.23)                   |  |  |

**Statistical analyses**

|                                         |                                                                                  |
|-----------------------------------------|----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | PFS (investigator's assessment) overall                                          |
| Comparison groups                       | Panobinostat + Bortezomib + Dexamethasone v Placebo + Bortezomib + Dexamethasone |
| Number of subjects included in analysis | 768                                                                              |
| Analysis specification                  | Pre-specified                                                                    |
| Analysis type                           | superiority                                                                      |
| P-value                                 | < 0.0001                                                                         |
| Method                                  | Logrank                                                                          |
| Parameter estimate                      | Cox proportional hazard                                                          |
| Point estimate                          | 0.63                                                                             |
| Confidence interval                     |                                                                                  |
| level                                   | 95 %                                                                             |
| sides                                   | 2-sided                                                                          |
| lower limit                             | 0.52                                                                             |
| upper limit                             | 0.76                                                                             |



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**Secondary: Final analysis of overall survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone**

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|                 |                                                                                                                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Final analysis of overall survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Number of OS events

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

End point timeframe:

Survival follow-up continued until 415 survival events had occurred. Data cut off was 29-Jun-2015 and the last patient last visit was on 30-Jul-2015.

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| End point values            | Panobinostat +<br>Bortezomib +<br>Dexamethasone | Placebo +<br>Bortezomib +<br>Dexamethasone |  |  |
|-----------------------------|-------------------------------------------------|--------------------------------------------|--|--|
| Subject group type          | Reporting group                                 | Reporting group                            |  |  |
| Number of subjects analysed | 387                                             | 381                                        |  |  |
| Units: Number of OS events  | 204                                             | 211                                        |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Final analysis of overall survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone**

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|                 |                                                                                                                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Final analysis of overall survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

survival time in months

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

End point timeframe:

Survival follow-up continued until 415 survival events had occurred. Data cut off was 29-Jun-2015 and the last patient last visit was on 30-Jul-2015.

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| End point values                 | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|----------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type               | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed      | 387                                       | 381                                  |  |  |
| Units: months                    |                                           |                                      |  |  |
| median (confidence interval 95%) | 40.28 (35.02 to 44.81)                    | 35.78 (28.98 to 40.64)               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall response rate in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

|                        |                                                                                                                                                                                                |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Overall response rate in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. |
| End point description: | Best overall response based on mEBMT criteria per investigator assessment                                                                                                                      |
| End point type         | Secondary                                                                                                                                                                                      |
| End point timeframe:   | 45 months                                                                                                                                                                                      |

| End point values                    | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|-------------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type                  | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed         | 387                                       | 381                                  |  |  |
| Units: % participants with response |                                           |                                      |  |  |
| number (not applicable)             | 60.7                                      | 54.6                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to response per investigator assessment (mEBMT criteria) of response patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

|                 |                                                                                                                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to response per investigator assessment (mEBMT criteria) of response patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:  
45 months

| End point values                  | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|-----------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type                | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed       | 387                                       | 381                                  |  |  |
| Units: time to response in months |                                           |                                      |  |  |
| median (confidence interval 95%)  | 1.51 (1.41 to 1.64)                       | 2 (1.61 to 2.79)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Duration of response per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.**

|                 |                                                                                                                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Duration of response per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:  
45 months

| End point values                      | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|---------------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type                    | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed           | 387                                       | 381                                  |  |  |
| Units: duration of response in months |                                           |                                      |  |  |
| median (confidence interval 95%)      | 13.14 (11.76 to 14.92)                    | 10.87 (9.23 to 11.76)                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to progression/relapse per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

|                 |                                                                                                                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to progression/relapse per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

45 months

| End point values                 | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|----------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type               | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed      | 387                                       | 381                                  |  |  |
| Units: response in months        |                                           |                                      |  |  |
| median (confidence interval 95%) | 12.71 (11.3 to 14.06)                     | 8.54 (7.66 to 9.72)                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: EORTC QLQ-MY20-Change from Baseline by treatment group

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | EORTC QLQ-MY20-Change from Baseline by treatment group |
|-----------------|--------------------------------------------------------|

End point description:

Higher values in the disease symptoms and side effects of treatment scores indicate worsening. Higher scores in the future perspective and body image scores indicate improvement. LS Means and SEM are estimated from the repeated measures model. Following factors and covariates are included in the repeated measurement model: time, treatment, treatment by time interaction, number of prior lines of anti-MM therapy (1/ 2 and 3), prior use of BTZ (Yes/ No), baseline score.

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

End point timeframe:

12, 24 and 48 weeks

| End point values                                     | Panobinostat +<br>Bortezomib +<br>Dexamethason<br>e | Placebo +<br>Bortezomib +<br>Dexamethason<br>e |  |  |
|------------------------------------------------------|-----------------------------------------------------|------------------------------------------------|--|--|
| Subject group type                                   | Reporting group                                     | Reporting group                                |  |  |
| Number of subjects analysed                          | 387                                                 | 381                                            |  |  |
| Units: score on a scale                              |                                                     |                                                |  |  |
| least squares mean (confidence interval<br>95%)      |                                                     |                                                |  |  |
| Disease Symptom wk 12 change<br>baseline (n=215,243) | -4.795 (-6.76<br>to -2.83)                          | -4.865 (-6.75<br>to -2.98)                     |  |  |
| Disease Symptom wk 24 change<br>baseline (n=148,177) | -4.401 (-6.53<br>to -2.27)                          | -6.797 (-8.79<br>to -4.81)                     |  |  |
| Disease Symptom wk 48 change<br>baseline (n=37,26)   | -2.836 (-6.76<br>to -1.084)                         | -6.626 (-11.1<br>to -2.12)                     |  |  |
| Side effects of treatment wk 12 chge<br>(n=213,242)  | 8.162 (6.51 to<br>9.814)                            | 5.524 (3.933<br>to 7.115)                      |  |  |
| Side effects of treatment wk 24 chge<br>(n=148,175)  | 9.016 (6.955<br>to 11.08)                           | 7.731 (5.795<br>to 9.668)                      |  |  |
| Side effects of treatment wk 48 chge<br>(n=37,26)    | 3.357 (0.442<br>to 6.273)                           | 3.654 (0.352<br>to 6.956)                      |  |  |
| Future perspective wk 12 chge<br>(n=214,242)         | 5.319 (2.893<br>to 7.744)                           | 6.194 (3.854<br>to 8.533)                      |  |  |
| Future perspective wk 24 chge<br>(n=148,176)         | 3.877 (0.977<br>to 6.778)                           | 5.839 (3.103<br>to 8.575)                      |  |  |
| Future perspective wk 48 chge<br>(n=37,26)           | 4.331 (-0.142<br>to 8.804)                          | 6.951 (1.807<br>to 12.1)                       |  |  |
| Body image wk 12 chge (n=213,240)                    | -7.178 (-10.5<br>to -3.87)                          | -6.22 (-9.41 to<br>-3.03)                      |  |  |
| Body image wk 24 chge (n=147,175)                    | -11.463 (-15.3<br>to -7.66)                         | -7.358 (-10.9<br>to -3.81)                     |  |  |
| Body image wk 48 chge (n=37,26)                      | -2.161 (-7.73<br>to 3.41)                           | -4.666 (-11.1<br>to 1.729)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: EORTC QLQ-C30 - Summary Statistics by treatment group

|                                                                                                                                                                                                                                                                                                                                                                   |                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                   | EORTC QLQ-C30 - Summary Statistics by treatment group |
| End point description:<br>The EORTC QLQ-C30 measures functional dimensions (physical, role, emotional, cognitive, and social), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), six single-item symptom scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale |                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                    | Secondary                                             |
| End point timeframe:<br>12, 24 and 48 weeks                                                                                                                                                                                                                                                                                                                       |                                                       |

| <b>End point values</b>                            | <b>Panobinostat +<br/>Bortezomib +<br/>Dexamethason<br/>e</b> | <b>Placebo +<br/>Bortezomib +<br/>Dexamethason<br/>e</b> |  |  |
|----------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|--|--|
| Subject group type                                 | Reporting group                                               | Reporting group                                          |  |  |
| Number of subjects analysed                        | 387                                                           | 381                                                      |  |  |
| Units: score on a scale                            |                                                               |                                                          |  |  |
| least squares mean (confidence interval<br>95%)    |                                                               |                                                          |  |  |
| Global health wk 12 change baseline<br>(n=216,239) | -9.853 (-12.5<br>to -7.2)                                     | -4.044 (-6.6 to<br>-1.49)                                |  |  |
| Global health wk 24 change baseline<br>(n=150,176) | -7.867 (-10.7<br>to -5.08)                                    | -1.518 (-4.11<br>to -1.075)                              |  |  |
| Global health wk 48 change baseline<br>(n=38,26)   | -2.986 (-7.21<br>to 1.237)                                    | 4.345 (-0.416<br>to 9.106)                               |  |  |
| Physical functioning wk 12 chge<br>(n=217,242)     | -9.67 (-12 to -<br>7.38)                                      | -5.393 (-76.3<br>to -3.16)                               |  |  |
| Physical functioning wk 24 chge<br>(n=151,177)     | -9.516 (-12.2<br>to -7.38)                                    | -6.456 (-8.98<br>to -3.93)                               |  |  |
| Physical functioning wk 48 chge<br>(n=38,26)       | -2.88 (-6.41 to<br>0.651)                                     | 2.037 (-2.07 to<br>6.147)                                |  |  |
| Role functioning wk 12 chge<br>(n=215,237)         | -11.159 (-14.6<br>to -7.74)                                   | -6.762 (-10.1<br>to -3.45)                               |  |  |
| Role functioning wk 24 chge<br>(n=150,176)         | -11.875 (-15.7<br>to -8.01)                                   | -11.263 (-14.9<br>to -7.61)                              |  |  |
| Role functioning wk 48 chge (n=38,26)              | -5.927 (-11.4<br>to -0.424)                                   | -0.401 (-6.73<br>to 5.924)                               |  |  |
| Cognitive functioning wk 12 chge<br>(n=216,240)    | -4.464 (-6.89<br>to -2.04)                                    | -1.023 (-3.36<br>to 1.318)                               |  |  |
| Cognitive functioning wk 24 chge<br>(n=149,176)    | -6.053 (-8.87<br>to -3.24)                                    | -3.542 (-6.22<br>to -0.865)                              |  |  |
| Cognitive functioning wk 48 chge<br>(n=38,26)      | -5.568 (-9.79<br>to -1.34)                                    | -4.042 (-8.99<br>to 0.902)                               |  |  |
| Social functioning wk 12 chge<br>(n=216,240)       | -8.502 (-11.6<br>to -5.44)                                    | -3.991 (-6.97<br>to 1.02)                                |  |  |
| Social functioning wk 24 chge<br>(n=148,171)       | -8.925 (-12.4<br>to -5.42)                                    | -6.338 (-9.66<br>to -3.02)                               |  |  |
| Social functioning wk 48 chge<br>(n=37,26)         | -6.104 (-11 to<br>-1.22)                                      | 4.617 (-0.93 to<br>10.16)                                |  |  |
| Fatigue wk 12 chge (n=217,241)                     | 15.122 (12.27<br>to 17.98)                                    | 7.939 (5.174<br>to 10.7)                                 |  |  |
| Fatigue wk 24 chge (n=151,176)                     | 12.677 (9.419<br>to 15.94)                                    | 9.203 (6.136<br>to 12.27)                                |  |  |
| Fatigue wk 48 chge(n=38,26)                        | 4.646 (0.086<br>to 9.206)                                     | -2.625 (-7.88<br>to 2.628)                               |  |  |
| Dyspnea wk 12 chge (n=217,240)                     | 13.964 (10.6<br>to 17.33)                                     | 6.266 (3.012<br>to 9.521)                                |  |  |
| Dyspnea wk 24 chge (n=151,177)                     | 7.939 (4.639<br>to 11.24)                                     | 5.308 (2.221<br>to 8.394)                                |  |  |
| Dyspnea wk 48 chge (n=38,26)                       | 4.118 (-1.58 to<br>9.813)                                     | 2.82 (-3.88 to<br>9.523)                                 |  |  |
| Insomnia wk 12 chge (n=216,239)                    | 6.283 (2.851<br>to 9.715)                                     | 7.625 (4.331<br>to 10.92)                                |  |  |
| Insomnia wk 24 chge (n=149,176)                    | 10.023 (6.038<br>to 14.01)                                    | 6.104 (2.381<br>to 9.827)                                |  |  |
| Insomnia wk 48 chge (n=38,26)                      | -2.464 (-8.74<br>to 3.811)                                    | -3.442 (-10.9<br>to 4.017)                               |  |  |
| Appetite loss wk 12 chge (n=217,239)               | 15.167 (11.6<br>to 18.74)                                     | 5.383 (1.925<br>to 8.841)                                |  |  |
| Appetite loss wk 24 chge (n=151,176)               | 16.574 (12.39<br>to 20.76)                                    | 5.861 (1.918<br>to 9.804)                                |  |  |

|                                     |                         |                         |  |  |
|-------------------------------------|-------------------------|-------------------------|--|--|
| Appetite loss wk 48 chge (n=38,26)  | 3.999 (-2.08 to 10.07)  | -2.963 (-9.99 to 4.061) |  |  |
| Constipation wk 12 chge (n=215,240) | 4.135 (0.667 to 7.603)  | 6.42 (3.104 to 9.735)   |  |  |
| Constipation wk 24 chge (n=151,177) | -0.153 (-3.64 to 3.337) | 0.524 (-2.73 to 5.782)  |  |  |
| Constipation wk 48 chge (n=38,25)   | -0.358 (-5.57 to 4.851) | -0.946 (-7.26 to 5.373) |  |  |
| Diarrhea wk 12 chge (n=217,241)     | 18.888 (15.04 to 22.74) | 10.206 (6.452 to 13.96) |  |  |
| Diarrhea wk 24 chge (n=150,177)     | 23.163 (18.46 to 27.87) | 16.406 (11.98 to 20.83) |  |  |
| Diarrhea wk 48 chge (n=38,26)       | 20.48 (14.02 to 26.94)  | 10.996 (3.422 to 18.57) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) Change from Baseline by treatment group

|                 |                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Functional Assessment of Cancer Therapy/Gynecologic Oncology Group- Neurotoxicity (FACT/GOG-NTX) Change from Baseline by treatment group |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The FACT/GOG-NTX was developed from the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System and focuses on four general quality of life domains for physical well being, functional wellbeing, social/family well-being, and emotional well-being, and includes additional items to characterize treatment-related neurotoxicity. Higher subscales/total scores represent higher QOL. In the case of the neurotoxicity subscale, lower scores correspond to higher neurotoxicity. The recall period referenced in the questionnaire is the past 7 days. Ranges for FACT-G subscales are as follows: PWB, SWB and FWB scale 0-28, EWB scale 0-24, NtxS scale 0-44, FACT/GOG-Ntx trial outcome index scale is 0-100 and FACT-G scale is also scaled 0-100. An increase from baseline in these scores indicate improvement.

|                      |                     |
|----------------------|---------------------|
| End point type       | Secondary           |
| End point timeframe: | 12, 24 and 48 weeks |

| End point values                                | Panobinostat + Bortezomib + Dexamethasone | Placebo + Bortezomib + Dexamethasone |  |  |
|-------------------------------------------------|-------------------------------------------|--------------------------------------|--|--|
| Subject group type                              | Reporting group                           | Reporting group                      |  |  |
| Number of subjects analysed                     | 387                                       | 381                                  |  |  |
| Units: score on a scale                         |                                           |                                      |  |  |
| least squares mean (confidence interval 95%)    |                                           |                                      |  |  |
| Neurotoxicity wk 12 change baseline (n=212,240) | -4.481 (-5.33 to -3.63)                   | -3.337 (-4.17 to -2.5)               |  |  |

|                                                 |                          |                          |  |  |
|-------------------------------------------------|--------------------------|--------------------------|--|--|
| Neurotoxicity wk 24 change baseline (n=148,174) | -4.564 (-5.49 to -3.64)  | -4.739 (-5.61 to -3.86)  |  |  |
| Neurotoxicity wk 48 change baseline (n=35,26)   | -3.158 (-4.52 to -1.79)  | -2.133 (-3.64 to -0.627) |  |  |
| Physical wellbeing wk 12 chge (n=215,240)       | -3.29 (-3.94 to -2.64)   | -1.952 (-2.58 to -1.32)  |  |  |
| Physical wellbeingwk 24 chge (n=150,176)        | -3.044 (-3.74 to -2.35)  | -2.259 (-2.92 to -1.6)   |  |  |
| Physical wellbeing wk 48 chge (n=38,26)         | -2.037 (-3.08 to -0.992) | 0.203 (-1.03 to 1.439)   |  |  |
| Trial Outcomes wk 12 chge (n=209,236)           | -10.573 (-12.2 to -8.86) | -6.874 (-8.55 to -5.19)  |  |  |
| Trial Outcomes wk 24 chge (n=148,173)           | -9.84 (-11.7 to -7.98)   | -8.894 (-10.7 to -7.13)  |  |  |
| Trial Outcomes wk 48 chge (n=35,26)             | -6.633 (-9.28 to -3.98)  | -2.821 (-5.76 to 0.122)  |  |  |
| FACT-G Total wk 12 chge (n=213,240)             | -6.658 (-8.23 to -5.09)  | -4.106 (-5.64 to -2.57)  |  |  |
| FACT-G Totalwk 24 chge (n=147,175)              | -6.076 (-7.84 to -4.31)  | -4.609 (-6.3 to -2.92)   |  |  |
| FACT-G Total wk 48 chge (n=37,26)               | -2.704 (-5.29 to -0.118) | -1.435 (-4.42 to 1.547)  |  |  |
| FACT/GOGNTX Total wk 12 chge (n=206,230)        | -11.176 (-13.3 to -9.03) | -7.524 (-9.64 to -5.41)  |  |  |
| FACT/GOGNTX Total wk 24 chge (n=146,172)        | -10.581 (-12.9 to -8.23) | -9.179 (-9.64 to -5.41)  |  |  |
| FACT/GOGNTX Total wk 48 chge (n=35,26)          | -5.871 (-9.24 to -2.5)   | -3.151 (-6.92 to 0.614)  |  |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | PAN+BTZ+Dex |
|-----------------------|-------------|

Reporting group description:

PAN+BTZ+Dex

|                       |             |
|-----------------------|-------------|
| Reporting group title | PBO+BTZ+Dex |
|-----------------------|-------------|

Reporting group description:

PBO+BTZ+Dex

| Serious adverse events                                              | PAN+BTZ+Dex        | PBO+BTZ+Dex        |  |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed                                         | 228 / 381 (59.84%) | 157 / 377 (41.64%) |  |
| number of deaths (all causes)                                       | 30                 | 18                 |  |
| number of deaths resulting from adverse events                      | 7                  | 2                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Cancer pain                                                         |                    |                    |  |
| subjects affected / exposed                                         | 0 / 381 (0.00%)    | 1 / 377 (0.27%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Endometrial cancer                                                  |                    |                    |  |
| subjects affected / exposed                                         | 1 / 381 (0.26%)    | 0 / 377 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Prostate cancer                                                     |                    |                    |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small cell lung cancer                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic stenosis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 381 (1.31%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypovolaemic shock                              |                 |                 |  |

|                                                      |                  |                 |  |
|------------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                          | 3 / 381 (0.79%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Lymphoedema                                          |                  |                 |  |
| subjects affected / exposed                          | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Orthostatic hypotension                              |                  |                 |  |
| subjects affected / exposed                          | 9 / 381 (2.36%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all      | 7 / 9            | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Shock haemorrhagic                                   |                  |                 |  |
| subjects affected / exposed                          | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 1 / 1            | 0 / 0           |  |
| Venous thrombosis limb                               |                  |                 |  |
| subjects affected / exposed                          | 1 / 381 (0.26%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General disorders and administration site conditions |                  |                 |  |
| Asthenia                                             |                  |                 |  |
| subjects affected / exposed                          | 15 / 381 (3.94%) | 6 / 377 (1.59%) |  |
| occurrences causally related to treatment / all      | 6 / 18           | 0 / 6           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Chest discomfort                                     |                  |                 |  |
| subjects affected / exposed                          | 1 / 381 (0.26%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Chills                                               |                  |                 |  |
| subjects affected / exposed                          | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Fatigue                                              |                  |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 11 / 381 (2.89%) | 2 / 377 (0.53%)  |  |
| occurrences causally related to treatment / all | 10 / 12          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)  | 0 / 377 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Generalised oedema                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypothermia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 2 / 377 (0.53%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multi-organ failure                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 1 / 377 (0.27%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 3 / 377 (0.80%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia                                         |                  |                  |  |
| subjects affected / exposed                     | 16 / 381 (4.20%) | 11 / 377 (2.92%) |  |
| occurrences causally related to treatment / all | 5 / 17           | 4 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sudden death                                    |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Benign prostatic hyperplasia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 1           |  |
| Aspiration                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Asthma                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough                                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%) | 7 / 377 (1.86%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 4 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoventilation                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung disorder                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infiltration                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orthopnoea                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 381 (1.05%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 5 / 381 (1.31%) | 4 / 377 (1.06%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pulmonary haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 381 (1.31%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Tachypnoea                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Delirium                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomania                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase                      |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| increased                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood lactate dehydrogenase increased           |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood potassium decreased                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood pressure decreased                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| C-reactive protein increased                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical condition abnormal             |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 381 (1.05%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| White blood cell count decreased                |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Accidental overdose                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hand fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intentional overdose                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Laceration                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transfusion reaction                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 1           |  |
| Cardiac failure                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiopulmonary failure                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pericardial effusion                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Altered state of consciousness                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Autonomic neuropathy                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain compression                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain injury                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Brain oedema                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central nervous system haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central nervous system necrosis                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Coma                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cranial nerve paralysis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Depressed level of consciousness                |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 381 (1.31%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage intracranial                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemiparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperreflexia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lacunar infarction                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 5 / 381 (1.31%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuralgia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy peripheral                           |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 381 (0.79%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyneuropathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post herpetic neuralgia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sensory loss                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Somnolence                                      |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Speech disorder                                 |                  |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Syncope                                         |                  |                 |  |
| subjects affected / exposed                     | 5 / 381 (1.31%)  | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 3 / 5            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Transient ischaemic attack                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| VIIth nerve paralysis                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood and lymphatic system disorders            |                  |                 |  |
| Anaemia                                         |                  |                 |  |
| subjects affected / exposed                     | 14 / 381 (3.67%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 10 / 15          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Febrile neutropenia                             |                  |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 3 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperviscosity syndrome                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Leukocytosis                                    |                  |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Leukopenia                                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Monocytosis                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neutropenia                                     |                  |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancytopenia                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombocytopenia                                |                  |                 |  |
| subjects affected / exposed                     | 28 / 381 (7.35%) | 8 / 377 (2.12%) |  |
| occurrences causally related to treatment / all | 28 / 35          | 6 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ear and labyrinth disorders                     |                  |                 |  |
| Vertigo                                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |
| Conjunctivitis                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Exophthalmos                                    |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Optic ischaemic neuropathy                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal discomfort                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal distension                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis                                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |

|                                                 |                   |                 |  |
|-------------------------------------------------|-------------------|-----------------|--|
| subjects affected / exposed                     | 43 / 381 (11.29%) | 9 / 377 (2.39%) |  |
| occurrences causally related to treatment / all | 35 / 54           | 7 / 10          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Dysphagia                                       |                   |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Faecaloma                                       |                   |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Gastric haemorrhage                             |                   |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)   | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Gastritis                                       |                   |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)   | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                   |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)   | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 1 / 2             | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                   |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Haematemesis                                    |                   |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Haematochezia                                   |                   |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 5 / 381 (1.31%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 4 / 5           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 7 / 381 (1.84%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 6 / 7           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrotising oesophagitis                        |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatitis                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatitis acute                              |                  |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Peritoneal necrosis                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rectal haemorrhage                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Subileus                                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                  |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vomiting                                        |                  |                 |  |
| subjects affected / exposed                     | 12 / 381 (3.15%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 11 / 12          | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatobiliary disorders                         |                  |                 |  |
| Biliary dyskinesia                              |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cirrhosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatomegaly                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Acute febrile neutrophilic dermatosis           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis allergic                             |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash                                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Swelling face                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 7 / 381 (1.84%) | 9 / 377 (2.39%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Anuria                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Azotaemia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oliguria                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%) | 5 / 377 (1.33%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal impairment                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ureteric obstruction                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint swelling                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myopathy                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis of jaw                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Acute tonsillitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspergillus infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atypical pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteriuria                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bronchopulmonary aspergillosis                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 381 (0.52%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus colitis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated tuberculosis                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis infectious                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 6 / 381 (1.57%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 2 / 6           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis salmonella                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal infection                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemophilus sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis B                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%) | 5 / 377 (1.33%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 381 (1.31%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 4 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Nasopharyngitis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrotising fasciitis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Oral candidiasis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parotitis                                       |                 |                 |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Periodontitis                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis                                     |                   |                   |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)   | 1 / 377 (0.27%)   |  |
| occurrences causally related to treatment / all | 2 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumococcal sepsis                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)   | 0 / 377 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 56 / 381 (14.70%) | 40 / 377 (10.61%) |  |
| occurrences causally related to treatment / all | 35 / 66           | 16 / 47           |  |
| deaths causally related to treatment / all      | 2 / 2             | 1 / 3             |  |
| Pneumonia bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)   | 2 / 377 (0.53%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia fungal                                |                   |                   |  |
| subjects affected / exposed                     | 2 / 381 (0.52%)   | 0 / 377 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia haemophilus                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)   | 1 / 377 (0.27%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia influenzal                            |                   |                   |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 381 (0.52%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia pneumococcal                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia respiratory syncytial viral           |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Salmonellosis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 9 / 381 (2.36%) | 7 / 377 (1.86%) |  |
| occurrences causally related to treatment / all | 3 / 9           | 1 / 7           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 9 / 381 (2.36%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 9           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal sepsis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 3 / 381 (0.79%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 8 / 381 (2.10%) | 4 / 377 (1.06%) |  |
| occurrences causally related to treatment / all | 2 / 11          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Varicella                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral haemorrhagic cystitis                     |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Viral infection                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Metabolism and nutrition disorders              |                  |                 |  |
| Acidosis                                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Decreased appetite                              |                  |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%)  | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 3 / 5            | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dehydration                                     |                  |                 |  |
| subjects affected / exposed                     | 11 / 381 (2.89%) | 5 / 377 (1.33%) |  |
| occurrences causally related to treatment / all | 4 / 12           | 2 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetes mellitus                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%)  | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Electrolyte imbalance                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%)  | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypercalcaemia                                  |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 3 / 377 (0.80%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypochloraemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 2 / 377 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 8 / 381 (2.10%) | 4 / 377 (1.06%) |  |
| occurrences causally related to treatment / all | 7 / 11          | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 381 (1.05%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypophagia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 381 (0.52%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypophosphataemia                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic acidosis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 381 (0.00%) | 1 / 377 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour lysis syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 381 (0.26%) | 0 / 377 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | PAN+BTZ+Dex        | PBO+BTZ+Dex        |  |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 379 / 381 (99.48%) | 366 / 377 (97.08%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypertension                                          |                    |                    |  |
| subjects affected / exposed                           | 28 / 381 (7.35%)   | 23 / 377 (6.10%)   |  |
| occurrences (all)                                     | 33                 | 36                 |  |
| Hypotension                                           |                    |                    |  |
| subjects affected / exposed                           | 49 / 381 (12.86%)  | 34 / 377 (9.02%)   |  |
| occurrences (all)                                     | 62                 | 38                 |  |
| Orthostatic hypotension                               |                    |                    |  |
| subjects affected / exposed                           | 22 / 381 (5.77%)   | 11 / 377 (2.92%)   |  |
| occurrences (all)                                     | 28                 | 15                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| Asthenia                                              |                    |                    |  |
| subjects affected / exposed                           | 77 / 381 (20.21%)  | 51 / 377 (13.53%)  |  |
| occurrences (all)                                     | 132                | 70                 |  |
| Fatigue                                               |                    |                    |  |
| subjects affected / exposed                           | 155 / 381 (40.68%) | 109 / 377 (28.91%) |  |
| occurrences (all)                                     | 217                | 161                |  |
| Oedema peripheral                                     |                    |                    |  |

|                                                 |                    |                   |  |
|-------------------------------------------------|--------------------|-------------------|--|
| subjects affected / exposed                     | 104 / 381 (27.30%) | 69 / 377 (18.30%) |  |
| occurrences (all)                               | 147                | 88                |  |
| Pyrexia                                         |                    |                   |  |
| subjects affected / exposed                     | 90 / 381 (23.62%)  | 48 / 377 (12.73%) |  |
| occurrences (all)                               | 137                | 60                |  |
| Respiratory, thoracic and mediastinal disorders |                    |                   |  |
| Cough                                           |                    |                   |  |
| subjects affected / exposed                     | 81 / 381 (21.26%)  | 70 / 377 (18.57%) |  |
| occurrences (all)                               | 110                | 96                |  |
| Dyspnoea                                        |                    |                   |  |
| subjects affected / exposed                     | 53 / 381 (13.91%)  | 40 / 377 (10.61%) |  |
| occurrences (all)                               | 59                 | 51                |  |
| Productive cough                                |                    |                   |  |
| subjects affected / exposed                     | 18 / 381 (4.72%)   | 19 / 377 (5.04%)  |  |
| occurrences (all)                               | 25                 | 27                |  |
| Psychiatric disorders                           |                    |                   |  |
| Insomnia                                        |                    |                   |  |
| subjects affected / exposed                     | 73 / 381 (19.16%)  | 61 / 377 (16.18%) |  |
| occurrences (all)                               | 89                 | 64                |  |
| Investigations                                  |                    |                   |  |
| Alanine aminotransferase increased              |                    |                   |  |
| subjects affected / exposed                     | 22 / 381 (5.77%)   | 19 / 377 (5.04%)  |  |
| occurrences (all)                               | 30                 | 36                |  |
| Blood creatinine increased                      |                    |                   |  |
| subjects affected / exposed                     | 37 / 381 (9.71%)   | 21 / 377 (5.57%)  |  |
| occurrences (all)                               | 71                 | 29                |  |
| Blood urea increased                            |                    |                   |  |
| subjects affected / exposed                     | 20 / 381 (5.25%)   | 10 / 377 (2.65%)  |  |
| occurrences (all)                               | 46                 | 21                |  |
| Platelet count decreased                        |                    |                   |  |
| subjects affected / exposed                     | 44 / 381 (11.55%)  | 17 / 377 (4.51%)  |  |
| occurrences (all)                               | 82                 | 31                |  |
| Weight decreased                                |                    |                   |  |
| subjects affected / exposed                     | 44 / 381 (11.55%)  | 17 / 377 (4.51%)  |  |
| occurrences (all)                               | 49                 | 17                |  |
| Nervous system disorders                        |                    |                   |  |

|                                      |                    |                    |  |
|--------------------------------------|--------------------|--------------------|--|
| Dizziness                            |                    |                    |  |
| subjects affected / exposed          | 66 / 381 (17.32%)  | 61 / 377 (16.18%)  |  |
| occurrences (all)                    | 84                 | 95                 |  |
| Dysgeusia                            |                    |                    |  |
| subjects affected / exposed          | 36 / 381 (9.45%)   | 26 / 377 (6.90%)   |  |
| occurrences (all)                    | 39                 | 27                 |  |
| Headache                             |                    |                    |  |
| subjects affected / exposed          | 51 / 381 (13.39%)  | 40 / 377 (10.61%)  |  |
| occurrences (all)                    | 67                 | 65                 |  |
| Hypoaesthesia                        |                    |                    |  |
| subjects affected / exposed          | 29 / 381 (7.61%)   | 34 / 377 (9.02%)   |  |
| occurrences (all)                    | 33                 | 39                 |  |
| Neuralgia                            |                    |                    |  |
| subjects affected / exposed          | 38 / 381 (9.97%)   | 44 / 377 (11.67%)  |  |
| occurrences (all)                    | 51                 | 57                 |  |
| Neuropathy peripheral                |                    |                    |  |
| subjects affected / exposed          | 117 / 381 (30.71%) | 133 / 377 (35.28%) |  |
| occurrences (all)                    | 145                | 178                |  |
| Paraesthesia                         |                    |                    |  |
| subjects affected / exposed          | 24 / 381 (6.30%)   | 27 / 377 (7.16%)   |  |
| occurrences (all)                    | 29                 | 37                 |  |
| Peripheral sensory neuropathy        |                    |                    |  |
| subjects affected / exposed          | 42 / 381 (11.02%)  | 46 / 377 (12.20%)  |  |
| occurrences (all)                    | 49                 | 64                 |  |
| Polyneuropathy                       |                    |                    |  |
| subjects affected / exposed          | 28 / 381 (7.35%)   | 28 / 377 (7.43%)   |  |
| occurrences (all)                    | 35                 | 36                 |  |
| Blood and lymphatic system disorders |                    |                    |  |
| Anaemia                              |                    |                    |  |
| subjects affected / exposed          | 155 / 381 (40.68%) | 125 / 377 (33.16%) |  |
| occurrences (all)                    | 305                | 231                |  |
| Leukopenia                           |                    |                    |  |
| subjects affected / exposed          | 61 / 381 (16.01%)  | 31 / 377 (8.22%)   |  |
| occurrences (all)                    | 173                | 77                 |  |
| Lymphopenia                          |                    |                    |  |

|                             |                    |                    |  |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 52 / 381 (13.65%)  | 35 / 377 (9.28%)   |  |
| occurrences (all)           | 149                | 113                |  |
| Neutropenia                 |                    |                    |  |
| subjects affected / exposed | 112 / 381 (29.40%) | 40 / 377 (10.61%)  |  |
| occurrences (all)           | 296                | 102                |  |
| Thrombocytopenia            |                    |                    |  |
| subjects affected / exposed | 238 / 381 (62.47%) | 150 / 377 (39.79%) |  |
| occurrences (all)           | 697                | 342                |  |
| Eye disorders               |                    |                    |  |
| Conjunctivitis              |                    |                    |  |
| subjects affected / exposed | 28 / 381 (7.35%)   | 31 / 377 (8.22%)   |  |
| occurrences (all)           | 32                 | 36                 |  |
| Gastrointestinal disorders  |                    |                    |  |
| Abdominal distension        |                    |                    |  |
| subjects affected / exposed | 30 / 381 (7.87%)   | 26 / 377 (6.90%)   |  |
| occurrences (all)           | 32                 | 31                 |  |
| Abdominal pain              |                    |                    |  |
| subjects affected / exposed | 50 / 381 (13.12%)  | 38 / 377 (10.08%)  |  |
| occurrences (all)           | 76                 | 44                 |  |
| Abdominal pain upper        |                    |                    |  |
| subjects affected / exposed | 43 / 381 (11.29%)  | 36 / 377 (9.55%)   |  |
| occurrences (all)           | 54                 | 51                 |  |
| Constipation                |                    |                    |  |
| subjects affected / exposed | 102 / 381 (26.77%) | 122 / 377 (32.36%) |  |
| occurrences (all)           | 135                | 159                |  |
| Diarrhoea                   |                    |                    |  |
| subjects affected / exposed | 254 / 381 (66.67%) | 157 / 377 (41.64%) |  |
| occurrences (all)           | 655                | 342                |  |
| Dyspepsia                   |                    |                    |  |
| subjects affected / exposed | 47 / 381 (12.34%)  | 43 / 377 (11.41%)  |  |
| occurrences (all)           | 52                 | 54                 |  |
| Nausea                      |                    |                    |  |
| subjects affected / exposed | 138 / 381 (36.22%) | 78 / 377 (20.69%)  |  |
| occurrences (all)           | 212                | 118                |  |
| Vomiting                    |                    |                    |  |



|                                                                                                                   |                          |                         |  |
|-------------------------------------------------------------------------------------------------------------------|--------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                  | 91 / 381 (23.88%)<br>141 | 47 / 377 (12.47%)<br>54 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 33 / 381 (8.66%)<br>40   | 23 / 377 (6.10%)<br>32  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 25 / 381 (6.56%)<br>28   | 26 / 377 (6.90%)<br>35  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 45 / 381 (11.81%)<br>51  | 46 / 377 (12.20%)<br>51 |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 21 / 381 (5.51%)<br>24   | 31 / 377 (8.22%)<br>37  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                                                 | 23 / 381 (6.04%)<br>29   | 21 / 377 (5.57%)<br>25  |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)                                             | 24 / 381 (6.30%)<br>26   | 20 / 377 (5.31%)<br>21  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                                                       | 24 / 381 (6.30%)<br>32   | 24 / 377 (6.37%)<br>30  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                             | 40 / 381 (10.50%)<br>47  | 54 / 377 (14.32%)<br>61 |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 20 / 381 (5.25%)<br>23   | 25 / 377 (6.63%)<br>28  |  |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                                                 | 15 / 381 (3.94%)<br>16   | 36 / 377 (9.55%)<br>42  |  |
| Nasopharyngitis                                                                                                   |                          |                         |  |

|                                    |                    |                   |  |
|------------------------------------|--------------------|-------------------|--|
| subjects affected / exposed        | 49 / 381 (12.86%)  | 43 / 377 (11.41%) |  |
| occurrences (all)                  | 59                 | 60                |  |
| Respiratory tract infection        |                    |                   |  |
| subjects affected / exposed        | 17 / 381 (4.46%)   | 20 / 377 (5.31%)  |  |
| occurrences (all)                  | 27                 | 39                |  |
| Upper respiratory tract infection  |                    |                   |  |
| subjects affected / exposed        | 66 / 381 (17.32%)  | 54 / 377 (14.32%) |  |
| occurrences (all)                  | 104                | 84                |  |
| Urinary tract infection            |                    |                   |  |
| subjects affected / exposed        | 23 / 381 (6.04%)   | 15 / 377 (3.98%)  |  |
| occurrences (all)                  | 30                 | 19                |  |
| Metabolism and nutrition disorders |                    |                   |  |
| Decreased appetite                 |                    |                   |  |
| subjects affected / exposed        | 106 / 381 (27.82%) | 46 / 377 (12.20%) |  |
| occurrences (all)                  | 152                | 58                |  |
| Hyperglycaemia                     |                    |                   |  |
| subjects affected / exposed        | 30 / 381 (7.87%)   | 25 / 377 (6.63%)  |  |
| occurrences (all)                  | 53                 | 46                |  |
| Hypoalbuminaemia                   |                    |                   |  |
| subjects affected / exposed        | 21 / 381 (5.51%)   | 8 / 377 (2.12%)   |  |
| occurrences (all)                  | 32                 | 8                 |  |
| Hypocalcaemia                      |                    |                   |  |
| subjects affected / exposed        | 35 / 381 (9.19%)   | 32 / 377 (8.49%)  |  |
| occurrences (all)                  | 60                 | 46                |  |
| Hypokalaemia                       |                    |                   |  |
| subjects affected / exposed        | 100 / 381 (26.25%) | 53 / 377 (14.06%) |  |
| occurrences (all)                  | 197                | 91                |  |
| Hyponatraemia                      |                    |                   |  |
| subjects affected / exposed        | 48 / 381 (12.60%)  | 18 / 377 (4.77%)  |  |
| occurrences (all)                  | 77                 | 29                |  |
| Hypophosphataemia                  |                    |                   |  |
| subjects affected / exposed        | 42 / 381 (11.02%)  | 32 / 377 (8.49%)  |  |
| occurrences (all)                  | 91                 | 98                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30 June 2010     | This amendment was a local, country-specific amendment for Japan whose main purpose was to include hospitalization of Japanese patients during the first cycle of treatment in order to comply with the local bortezomib label. Secondly, this amendment included PK sampling on Cycle 1 Day 1 and Cycle 1 Day 8 in Japanese patients. Thirdly, this amendment added the commercially available dosage form of bortezomib available in Japan as part of the global protocol. As of the release date of this amendment, 34 patients had been randomized worldwide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 22 December 2011 | As of 17-Nov-2011, 668 patients had been randomized worldwide. This amendment was a global amendment to adjust the sample size to compensate for a higher than expected drop-out rate in the absence of any safety concerns. The study design was based on the best available information from the literature, other ongoing panobinostat trials, historical data and expert opinion. A review of blinded data concluded that the drop-out rate was higher than originally assumed. The main reason for the drop-out rate was that patients who discontinued treatment withdrew their consent to be followed for response assessment as per protocol. As a consequence, the expected drop-out rate as written in the statistical section of the original protocol needed to be updated. The sample size was therefore recalculated in order to attain the targeted number of PFS events while maintaining the original statistical assumptions. In addition to the increased sample size, an operational action plan for new and ongoing patients was put into place to follow patients for disease assessment after treatment discontinuation                                                                                                                                                                                  |
| 07 March 2012    | This amendment is a global amendment to enhance robustness of analysis at the second interim analysis (IA2), in order to provide a more precise estimate of the treatment effect and to increase probability of detecting a treatment effect at IA2. Consequently, this amendment increases the event (PFS) fraction for IA2 from 67% to 80% (306 to 368 events). In case the study is stopped at IA2 with higher fraction of the planned PFS events, the risk of an overestimation of the treatment effect would be reduced. As outlined in the statistical design, the group-sequential plan of the original CLBH589D2308 protocol stipulated two interim analyses corresponding to the time point when 33% (IA1:153 PFS events) and 67% (IA2:306 PFS events) of the total planned 460 PFS events have occurred. These time points were expected 13 months after start of randomization for IA1, 20 months for IA2, and 29 months for the final PFS analysis, respectively under the assumption of 30 patients / month accrual and 10% dropout rate. In this amendment the assumptions on the treatment effect (HR 0.74) are unchanged. The power to detect the treatment effect and to stop the study at IA2 for efficacy is increased from 53% to 71%. The cumulative type I error is unchanged (less than 5 %, two-sided). |
| 02 October 2012  | The main aim of this global amendment is to clarify that the collection of serum calcium variables (ionized serum calcium and/or total serum calcium and serum albumin for the derivation of albumin-adjusted serum calcium) should continue after the end of treatment until the end of follow-up for disease evaluations. The collection of these variables is already described in the Novartis Guidelines for response assessment in Multiple Myeloma (Post-text supplement 2), and is mandatory to identify hypercalcemia as part of progressive disease and relapse criteria, during treatment phase and for all patients who have entered or will enter post-treatment disease evaluations.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 May 2013    | For efficacy assessments, the study protocol requires measurement of the monoclonal protein (M-protein) spike by protein electrophoresis (PEP) in serum and urine as per modified EBMT criteria. Sites participating in the study used their local laboratories to perform the M-protein assessments. However, it was recently identified, that some study patients were monitored using either PEP without specific measurement of the M-protein spike (e.g. globulin gamma fraction was used as indicator for M-component IgG) or by alternative methods, other than PEP (e.g. nephelometric quantification of immunoglobulin levels). Although these methods are used in routine clinical practice, they are not a part of mEBMT criteria. The objective of this protocol amendment is: a. to document use of PEP results without specific measurement of the M-protein spike. b. to document use of measurement methods other than PEP (e.g. nephelometry) Regardless of the method used before this amendment, patients should continue to be followed with the same method throughout the study to ensure intra-patient consistency. The primary PFS analysis remains based on the Investigator's response assessment following the ITT principle. The newly collected data will be used in sensitivity analyses of PFS and other efficacy related endpoints, including an analysis using independent response assessment in patients for whom M-protein was not measured by electrophoresis or electrophoresis was used without measurement of M-protein spike. This specific assessment will be done by an Independent Review Committee (IRC). Detailed instructions on the independent review process will be included in the IRC Charter. Additional sensitivity analyses will be presented in detail in the Report Analysis Plan. |
| 21 August 2014 | Based on the trial's positive outcome for the final analysis of the primary endpoint PFS, Novartis has submitted the study results to several health authorities seeking regulatory approval of panobinostat in multiple myeloma. Overall survival (OS) is a key secondary endpoint in this study. The final analysis of OS is planned to be performed when approximately 415 survival events have been documented. The main purpose of this amendment is to introduce an additional (fourth) OS interim analysis when approximately 90% of the targeted number of OS events have been reached, in order to support the benefit/risk assessment of the studied investigational treatment prior to the final OS analysis, as agreed with the FDA. The OS alpha spending function for the additional IA and the final analysis will be adjusted to ensure control of the overall type I error.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported