



## Clinical trial results:

### **AFFIRM: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy**

#### **Summary**

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2009-013174-41       |
| Trial protocol           | BE GB FR ES DE AT IT |
| Global end of trial date | 02 November 2017     |

#### **Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 03 November 2018 |
| First version publication date | 06 January 2017  |
| Version creation reason        |                  |

#### **Trial information**

##### **Trial identification**

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | CRPC2 (C3431010) |
|-----------------------|------------------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00974311 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### **Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Pfizer Inc.   |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, 10017   |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com  |

Notes:

##### **Paediatric regulatory details**

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 20 February 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 02 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival.

Protection of trial subjects:

The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 30 September 2009 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 5 Years           |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Argentina: 10       |
| Country: Number of subjects enrolled | Australia: 93       |
| Country: Number of subjects enrolled | Austria: 25         |
| Country: Number of subjects enrolled | Belgium: 45         |
| Country: Number of subjects enrolled | Canada: 107         |
| Country: Number of subjects enrolled | Chile: 11           |
| Country: Number of subjects enrolled | France: 273         |
| Country: Number of subjects enrolled | Germany: 86         |
| Country: Number of subjects enrolled | Italy: 30           |
| Country: Number of subjects enrolled | Netherlands: 46     |
| Country: Number of subjects enrolled | Poland: 11          |
| Country: Number of subjects enrolled | South Africa: 6     |
| Country: Number of subjects enrolled | Spain: 36           |
| Country: Number of subjects enrolled | United Kingdom: 132 |
| Country: Number of subjects enrolled | United States: 288  |
| Worldwide total number of subjects   | 1199                |
| EEA total number of subjects         | 684                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 362 |
| From 65 to 84 years                       | 819 |
| 85 years and over                         | 18  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 1199 subjects were enrolled and randomized for double-blind (DB) phase. Out of which, 159 subjects entered the optional open-label extension (OLE) phase.

### Pre-assignment

Screening details:

Subjects were randomized 2:1 to receive either Enzalutamide or Placebo in DB phase. All subjects who continued in OLE phase, received Enzalutamide.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | DB Phase (up to 24 months)      |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Double blind                    |
| Roles blinded                | Subject, Investigator, Assessor |

### Arms

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

Arm description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code | MDV3100      |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Enzalutamide was administered as oral capsules, once daily, up to a maximum of 36 months.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

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

Dosage and administration details:

Placebo matched to Enzalutamide was administered as oral capsules, once daily, up to a maximum of 36 months.

| Number of subjects in period 1 | Enzalutamide | Placebo |
|--------------------------------|--------------|---------|
| Started                        | 800          | 399     |
| Completed                      | 109          | 50      |
| Not completed                  | 691          | 349     |
| Consent withdrawn by subject   | 16           | 7       |
| Death                          | 561          | 298     |
| Unspecified                    | 1            | -       |
| Study Terminated by Sponsor    | 108          | 42      |
| Lost to follow-up              | 5            | 2       |

## Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | OLE Phase (up to 77 months) |
| Is this the baseline period? | No                          |
| Allocation method            | Not applicable              |
| Blinding used                | Not blinded                 |

## Arms

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

### Arm description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code | MDV3100      |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

### Dosage and administration details:

Enzalutamide was administered as oral capsules, once daily, up to a maximum of 88 months.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

### Arm description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

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

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**Dosage and administration details:**

Placebo matched to Enzalutamide was administered as oral capsules, once daily, up to a maximum of 88 months.

| <b>Number of subjects in period 2</b> | Enzalutamide | Placebo |
|---------------------------------------|--------------|---------|
| Started                               | 109          | 50      |
| Completed                             | 0            | 0       |
| Not completed                         | 109          | 50      |
| Consent withdrawn by subject          | 2            | 1       |
| Death                                 | 14           | 21      |
| Unspecified                           | 15           | 2       |
| Study Terminated by Sponsor           | 78           | 26      |

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Enzalutamide |
|-----------------------|--------------|

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

| Reporting group values                  | Enzalutamide | Placebo | Total |
|---|--------------|---------|-------|
| Number of subjects                      | 800          | 399     | 1199  |
| Age Categorical<br>Units: Subjects      |              |         |       |
| <=18 years                              | 0            | 0       | 0     |
| Between 18 and 65 years                 | 232          | 130     | 362   |
| >=65 years                              | 568          | 269     | 837   |
| Age Continuous<br>Units: years          |              |         |       |
| arithmetic mean                         | 68.8         | 68.6    |       |
| standard deviation                      | ± 7.96       | ± 8.39  | -     |
| Sex: Female, Male<br>Units: Subjects    |              |         |       |
| Female                                  | 0            | 0       | 0     |
| Male                                    | 800          | 399     | 1199  |
| Region of Enrollment<br>Units: Subjects |              |         |       |
| United States                           | 181          | 107     | 288   |
| Spain                                   | 23           | 13      | 36    |
| Austria                                 | 15           | 10      | 25    |
| Chile                                   | 6            | 5       | 11    |
| United Kingdom                          | 82           | 50      | 132   |
| Italy                                   | 20           | 10      | 30    |
| France                                  | 193          | 80      | 273   |
| Canada                                  | 82           | 25      | 107   |
| Argentina                               | 7            | 3       | 10    |
| Belgium                                 | 27           | 18      | 45    |
| Poland                                  | 7            | 4       | 11    |
| Australia                               | 60           | 33      | 93    |
| South Africa                            | 3            | 3       | 6     |
| Germany                                 | 62           | 24      | 86    |
| Netherlands                             | 32           | 14      | 46    |
| Ethnicity (NIH/OMB)<br>Units: Subjects  |              |         |       |

|   |     |     |      |
|---|-----|-----|------|
| Hispanic or Latino                        | 32  | 23  | 55   |
| Not Hispanic or Latino                    | 768 | 376 | 1144 |
| Unknown or Not Reported                   | 0   | 0   | 0    |
| Race (NIH/OMB)                            |     |     |      |
| Units: Subjects                           |     |     |      |
| American Indian or Alaska Native          | 1   | 1   | 2    |
| Asian                                     | 5   | 8   | 13   |
| Native Hawaiian or Other Pacific Islander | 1   | 0   | 1    |
| Black or African American                 | 27  | 20  | 47   |
| White                                     | 745 | 366 | 1111 |
| More than one race                        | 0   | 0   | 0    |
| Unknown or Not Reported                   | 21  | 4   | 25   |



## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Enzalutamide |
|-----------------------|--------------|

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

|                       |              |
|-----------------------|--------------|
| Reporting group title | Enzalutamide |
|-----------------------|--------------|

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Enzalutamide: DB + OLE Phase |
|----------------------------|------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Placebo: DB Phase |
|----------------------------|-------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months).

|                            |   |
|----------------------------|---|
| Subject analysis set title | Placebo (DB) /Enzalutamide 160 mg (OLE) Phase |
|----------------------------|---|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects who received placebo in DB phase, completed DB Phase and entered in optional OLE Phase, received Enzalutamide capsules 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 7.7 months).

### Primary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Survival was defined as time from randomization to death due to any cause. The duration of overall survival was right-censored for subjects who were lost to follow-up since randomization or not known to have died at the data analysis cut-off date (this included subjects who were known to have died after the data analysis cut-off date). Intent to treat (ITT) population included all subjects who were randomized into the study. The upper limit of the 95% confidence interval was not calculable because an

insufficient number of subjects reached the event at the final time point for assessment, and has been denoted by '99999'.

|  |         |
|--|---------|
| End point type                         | Primary |
| End point timeframe:                   |         |
| During study period (up to 101 months) |         |

| End point values                 | Enzalutamide         | Placebo             |  |  |
|----------------------------------|----------------------|---------------------|--|--|
| Subject group type               | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed      | 800                  | 399                 |  |  |
| Units: months                    |                      |                     |  |  |
| median (confidence interval 95%) | 18.4 (17.3 to 99999) | 13.6 (11.3 to 15.8) |  |  |

## Statistical analyses

| Statistical analysis title              | Enzalutamide vs. Placebo |
|---|--------------------------|
| Comparison groups                       | Enzalutamide v Placebo   |
| Number of subjects included in analysis | 1199                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | < 0.0001 <sup>[1]</sup>  |
| Method                                  | Logrank                  |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 0.63                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.53                     |
| upper limit                             | 0.75                     |

Notes:

[1] - Stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status and mean Brief Pain Inventory – Short Form score (Question #3).

Hazard Ratio and 95% confidence interval are from Cox regression model.

## Secondary: Radiographic Progression-Free Survival

|   |  |
|---|--|
| End point title   | Radiographic Progression-Free Survival |
| End point description:  |  |
| Radiographic progression-free survival was defined as time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Subjects were assessed for objective disease progression at regularly scheduled visits. The consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 were taken into consideration for the determination of disease progression. Radiographic disease progression was defined by Response Evaluation Criteria in Solid Tumours (RECIST) version (vs.) 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan. Progression at the first scheduled reassessment at Week 13 required a confirmatory scan 6 or more weeks later. Subjects who did not reach the endpoint were right censored at their last assessment. ITT population included all subjects who were randomized into the study. |  |
| End point type  | Secondary                              |
| End point timeframe:  |  |
| During DB phase (up to 24 months)   |  |

| End point values                 | Enzalutamide     | Placebo          |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 800              | 399              |  |  |
| Units: months                    |                  |                  |  |  |
| median (confidence interval 95%) | 8.3 (8.2 to 9.4) | 2.9 (2.8 to 3.4) |  |  |

## Statistical analyses

| Statistical analysis title              | Enzalutamide vs. Placebo |
|---|--------------------------|
| Comparison groups                       | Enzalutamide v Placebo   |
| Number of subjects included in analysis | 1199                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | < 0.0001 [2]             |
| Method                                  | Logrank                  |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 0.4                      |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.35                     |
| upper limit                             | 0.47                     |

Notes:

[2] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).

Hazard Ratio and 95% confidence interval are from Cox regression model.

## Secondary: Time to First Skeletal-Related Event

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Time to First Skeletal-Related Event |
|-----------------|--------------------------------------|

End point description:

The time to first skeletal-related event was defined as time from randomization to the occurrence of the first skeletal-related event. Subjects were assessed for skeletal-related events at regularly scheduled visits. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Subjects who did not reach the endpoint were right censored at their last assessment. ITT population included all subjects who were randomized into the study. The upper limit of the 95% confidence interval was not calculable because an insufficient number of subjects reached the event at the final time point for assessment, and has been denoted by '99999'.

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

End point timeframe:

During DB Phase (up to 24 months)

| End point values                 | Enzalutamide        | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 800                 | 399                 |  |  |
| Units: months                    |                     |                     |  |  |
| median (confidence interval 95%) | 16.7 (14.6 to 19.1) | 13.3 (9.9 to 99999) |  |  |

## Statistical analyses

| Statistical analysis title              | Enzalutamide vs. Placebo |
|---|--------------------------|
| Comparison groups                       | Enzalutamide v Placebo   |
| Number of subjects included in analysis | 1199                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | = 0.0001 <sup>[3]</sup>  |
| Method                                  | Logrank                  |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 0.69                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.566                    |
| upper limit                             | 0.835                    |

Notes:

[3] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).

Hazard Ratio and 95% confidence interval are from Cox regression model.

## Secondary: Percentage of Subjects who Were Responders for Functional Assessment of Cancer Therapy-Prostate (FACT-P)

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects who Were Responders for Functional Assessment of Cancer Therapy-Prostate (FACT-P) |
|-----------------|--|

End point description:

The FACT-P was a 39-item subject questionnaire which assessed physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and additional prostate cancer specific concerns (12 items). All items were scored from 0 (not at all) to 4 (very much). The sum of scores on all 5 domains constitutes the global FACT-P. The global/total FACT-P score ranged from 0 (worst) to 156 (best), higher scores indicate better health status. Responders were those subjects who had a 10-point improvement in their total FACT-P score, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart. Here, number of subjects analyzed signifies evaluable ITT that included all subjects who were part of the ITT population and had a global FACT-P score at baseline and at least 1 post-baseline assessment.

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

End point timeframe:

Baseline up to 24 months

| End point values                 | Enzalutamide        | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 651                 | 257                 |  |  |
| Units: percentage of subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 43.2 (39.3 to 47.1) | 18.3 (13.8 to 23.6) |  |  |

## Statistical analyses

| Statistical analysis title              | Enzalutamide vs. Placebo             |
|---|--------------------------------------|
| Comparison groups                       | Enzalutamide v Placebo               |
| Number of subjects included in analysis | 908                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | < 0.0001 <sup>[4]</sup>              |
| Method                                  | Cochran-Mantel-Haenszel              |
| Parameter estimate                      | Difference in Percentage of Subjects |
| Point estimate                          | 24.9                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 18.8                                 |
| upper limit                             | 30.9                                 |

Notes:

[4] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).

Confidence Interval based on standard normal approximation.

## Secondary: Time to Prostate-Specific Antigen (PSA) Progression

| End point title        | Time to Prostate-Specific Antigen (PSA) Progression   |
|------------------------|---|
| End point description: | Time to PSA progression was defined as time from randomization to PSA progression. Subjects who did not reach the endpoint were right censored at their last assessment. For subjects with PSA declines at Week 13, the PSA progression date was defined as the date that a greater than and equal to ( $\geq$ )25 percent (%) increase and an absolute increase of $\geq 2$ nanogram per milliliter (ng/mL) above the nadir was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later (required only if PSA progression did not occur at last PSA assessment). For subjects with no PSA declines at Week 13, PSA progression date was defined as the date that a $\geq 25\%$ increase and an absolute increase of $\geq 2$ ng/mL above the baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later (required only if PSA progression did not occur at last PSA assessment). ITT population included all subjects who were randomized into the study. |
| End point type         | Secondary   |
| End point timeframe:   | Baseline and at every study visit from Week 13 while on study drug (up to 24 months)  |

| End point values                 | Enzalutamide     | Placebo          |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 800              | 399              |  |  |
| Units: months                    |                  |                  |  |  |
| median (confidence interval 95%) | 8.3 (5.8 to 8.3) | 3.0 (2.9 to 3.7) |  |  |

## Statistical analyses

| Statistical analysis title              | Enzalutamide vs. Placebo |
|---|--------------------------|
| Comparison groups                       | Enzalutamide v Placebo   |
| Number of subjects included in analysis | 1199                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | < 0.0001 <sup>[5]</sup>  |
| Method                                  | Logrank                  |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 0.248                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.204                    |
| upper limit                             | 0.303                    |

Notes:

[5] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3). Hazard Ratio and 95% confidence interval are from Cox regression model.

## Secondary: Percentage of Subjects With Pain Palliation

| End point title          | Percentage of Subjects With Pain Palliation  |
|--------------------------|--|
| End point description:   | Proportion of subjects with pain palliation was assessed for subjects with a stable and sufficient pain burden at study entry. Pain burden was measured by question #3 of Brief Pain Inventory (short form). This scale measures pain on a 0 to 10 scale with 0 indicating no pain and 10 indicating pain as bad as you can imagine. Pain palliation at Week 13 was determined for proportion of men with baseline bone metastasis (es) who had baseline pain attributable to metastasis (es). Palliation was defined as $\geq 30\%$ reduction in average pain score at Week 13 compared to baseline without a $\geq 30\%$ increase in analgesic use. Here, number of subject analyzed signifies evaluable ITT that included subjects with metastatic bone disease at baseline; provided answers to Question #3 of Brief Pain Inventory - short form for a minimum of 4 out of 7 days in baseline run-in period; stable baseline pain; stable analgesic use; and had an average pain score during baseline run-in period of $\geq 4$ . |
| End point type           | Secondary  |
| End point timeframe:     |  |
| Baseline up to 24 months |  |

| End point values                 | Enzalutamide        | Placebo           |  |  |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type               | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed      | 49                  | 15                |  |  |
| Units: percentage of subjects    |                     |                   |  |  |
| number (confidence interval 95%) | 44.9 (30.7 to 59.8) | 6.7 (0.2 to 31.9) |  |  |

## Statistical analyses

| Statistical analysis title              | Enzalutamide vs. Placebo              |
|---|---------------------------------------|
| Comparison groups                       | Enzalutamide v Placebo                |
| Number of subjects included in analysis | 64                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           |                                       |
| P-value                                 | = 0.0079 <sup>[6]</sup>               |
| Method                                  | Cochran-Mantel-Haenszel               |
| Parameter estimate                      | Difference in Rate of Pain Palliation |
| Point estimate                          | 38.2                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 19.4                                  |
| upper limit                             | 57                                    |

Notes:

[6] - Stratified by baseline Eastern Cooperative Oncology Group performance status (0–1 vs. 2).  
Confidence Interval based on standard normal approximation.

## Secondary: Percentage of Subjects With Prostate Specific Antigen (PSA) Response

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Prostate Specific Antigen (PSA) Response |
|-----------------|--|

End point description:

Subjects were evaluable for PSA response rate if they had a PSA level measured at baseline and at least 1 post-baseline assessment. Both PSA responses of > 50% and > 90% were determined. PSA responses required confirmation with a subsequent assessment that was conducted at least 3 weeks later. Here, number of subject analyzed signifies evaluable ITT that included subjects who were part of the ITT Population and had a PSA level measured at baseline and at least 1 post-baseline assessment.

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

End point timeframe:

During DB phase (up to 24 months)

| End point values              | Enzalutamide    | Placebo         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 731             | 330             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| Decline >=50% from baseline   | 54              | 2               |  |  |
| Decline >=90% from baseline   | 25              | 1               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Soft-Tissue Objective Response

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Soft-Tissue Objective Response |
|-----------------|--|

End point description:

Best overall soft tissue response as assessed using RECIST vs.1.1 during study was summarized using investigators' response assessments and also derived response assessments by treatment group. Only subjects with measurable soft tissue disease at screening were included in this analysis. Subjects with measurable disease at screening are subjects who had at least 1 target lesion identified per RECIST vs.1.1 at screening. Percentage of subjects summarizes number of subjects with complete or partial objective response (%). Soft Tissue assessment based on Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (vs.1.1). Eur J Cancer 2009; 45:228-247. Here, number of subject analyzed signifies evaluable ITT with measurable disease that included subjects who were part of ITT population and had measurable soft tissue disease at screening, defined by at least 1 target lesion according to RECIST vs.1.1.

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

End point timeframe:

During DB phase (up to 24 months)

| End point values              | Enzalutamide    | Placebo         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 446             | 208             |  |  |
| Units: percentage of subjects | 29              | 4               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: European Quality of Life Five-Domain (EQ-5D) Scale

|                 |  |
|-----------------|--|
| End point title | European Quality of Life Five-Domain (EQ-5D) Scale |
|-----------------|--|

End point description:

EQ-5D: subject rated questionnaire to assess health-related quality of life in terms of a single utility or index score. Five parameters (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were assessed on 3-point categorical scale (1= no problems, 2= some/moderate problems and 3= severe problem). Score were transformed and resulted in a total EQ-5D score range of 0 (worst imaginable health state) to 100 (best imaginable health state), with higher scores indicating better health and quality of life. Here, number of subject analyzed signifies evaluable ITT that included subjects who were part of the ITT population and who were evaluable for EQ-5D.

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

End point timeframe:

Week 13



| End point values                     | Enzalutamide        | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 126                 | 55                  |  |  |
| Units: units on a scale              |                     |                     |  |  |
| arithmetic mean (standard deviation) | 67.2 ( $\pm$ 19.29) | 60.0 ( $\pm$ 19.26) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Circulating Tumor Cell (CTC) Conversion

|  |   |
|--|---|
| End point title  | Percentage of Subjects with Circulating Tumor Cell (CTC) Conversion |
| End point description:   |   |
| CTC conversion was assessed for subjects with baseline CTC counts of $\geq 5$ cells per 7.5 milliliter (mL) of blood. A CTC conversion was defined as a decline in the CTC count to less than ( $<$ ) 5 cells per 7.5 mL of blood. In this endpoint percentage of subjects with CTC conversion was reported. Here, number of subject analyzed signifies CTC evaluable population that included subjects with a baseline and at least 1 post baseline CTC assessment. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline up to 24 months   |   |

| End point values                 | Enzalutamide        | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 127                 | 62                  |  |  |
| Units: percentage of subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 48 (39.09 to 57.07) | 9.7 (3.63 to 19.88) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

|   |   |
|---|---|
| End point title   | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) |
| End point description:  |   |
| AE: any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. SAE: AE resulting in any of following outcome/deemed significant and jeopardized subjects/required treatment to prevent other AE outcomes for any other reason: death; initial/prolonged |   |

inpatient hospitalization;life-threatening experience(immediate risk of dying);persistent/significant disability/incapacity;congenital anomaly.TEAEs:events occurred between first dose of study drug and up to safety follow-up visit/initiation of another anti-neoplastic therapy, whichever occurred first(up to 101 months).AEs included both serious and non-serious AEs.Clinically significant physical examination abnormalities were reported as AEs.Safety population:all randomized subjects who received at least 1 dose of study drug.Unscheduled visit:performed at any time during study whenever necessary to assess for/follow-up on AEs, at subject's request/if deemed necessary by investigator.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

| End point values            | Enzalutamide:<br>DB + OLE<br>Phase | Placebo: DB<br>Phase | Placebo (DB)<br>/Enzalutamide<br>160 mg (OLE)<br>Phase |  |
|-----------------------------|------------------------------------|----------------------|--|--|
| Subject group type          | Subject analysis set               | Subject analysis set | Subject analysis set                                   |  |
| Number of subjects analysed | 800                                | 399                  | 50   |  |
| Units: subjects             |                                    |                      |  |  |
| AEs                         | 789                                | 390                  | 48   |  |
| SAEs                        | 319                                | 155                  | 25   |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects with Clinically Significant Changes in Vital Signs

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Clinically Significant Changes in Vital Signs |
|-----------------|---|

End point description:

Criteria for abnormalities in vital signs included: sitting/supine systolic blood pressure (SBP) values: absolute result greater than (>) 180 millimeter of mercury (mmHg) and >40 mmHg increase from baseline (BL) and < 90 mmHg and >30 mmHg decrease from BL; diastolic blood pressure (DBP) values: absolute result >105 mmHg and >30 mmHg increase from BL and absolute result < 50 mmHg and >20 mmHg decrease from BL; any abnormalities in SBP or DBP; heart rate values: absolute result > 120 beats per minute (bpm) and >30 bpm increase from BL and absolute result < 50 bpm and >20 bpm decrease from BL or any abnormalities in heart rate. Safety population was defined as all randomized subjects who received at least 1 dose of study drug. Unscheduled visit was performed at any time during the study whenever necessary to assess for/follow-up on AEs, at the subject's request/if deemed necessary by the investigator.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

| End point values                                      | Enzalutamide:<br>DB + OLE<br>Phase | Placebo: DB<br>Phase | Placebo (DB)<br>/Enzalutamide<br>160 mg (OLE)<br>Phase |  |
|---|------------------------------------|----------------------|--|--|
| Subject group type                                    | Subject analysis set               | Subject analysis set | Subject analysis set                                   |  |
| Number of subjects analysed                           | 800                                | 399                  | 50   |  |
| Units: subjects                                       |                                    |                      |  |  |
| SBP: >180 mmHg and >40 mmHg<br>Increase from BL       | 28                                 | 7                    | 1  |  |
| SBP: < 90 mmHg and >30 mmHg<br>Decrease from BL       | 13                                 | 5                    | 0  |  |
| DBP: >105 mmHg and >30 mmHg<br>Increase from BL       | 5                                  | 2                    | 0  |  |
| DBP: < 50 mmHg and >20 mmHg<br>Decrease from BL       | 13                                 | 3                    | 1  |  |
| Any abnormalities in SBP or DBP                       | 52                                 | 16                   | 2  |  |
| Heart Rate: > 120 bpm and >30 bpm<br>Increase from BL | 7                                  | 5                    | 0  |  |
| Heart Rate: < 50 bpm and >20 bpm<br>Decrease from BL  | 18                                 | 1                    | 0  |  |
| Any abnormalities in Heart Rate                       | 25                                 | 6                    | 0  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Subjects With Any Newly Clinically Significant Abnormal Finding in Electrocardiogram (ECG)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Any Newly Clinically Significant Abnormal Finding in Electrocardiogram (ECG) <sup>[7]</sup> |
|-----------------|---|

End point description:

Any new post baseline abnormality was defined as any abnormal ECG finding that appeared after baseline assessment which was not seen at the screening or baseline ECG assessment. Where, criteria of abnormality was QTcF interval > 470 millisecond (msec). Subjects were counted once only for a specific abnormality. This endpoint was planned to be analysed in double blind phase only. Safety population was defined as all randomized subjects who received at least 1 dose of study drug. Unscheduled visit was performed at any time during the study whenever necessary to assess for or follow-up on AEs, at the subject's request or if deemed necessary by the investigator.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, up to the end of DB phase or unscheduled visit (up to 24 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only arms which are applicable to the endpoint are reported.

| End point values            | Enzalutamide    | Placebo: DB<br>Phase |  |  |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed | 800             | 399                  |  |  |
| Units: subjects             | 28              | 13                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Subjects With Grade 3/4 Post-Baseline Laboratory Toxicity (Hematology and Chemistry)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Grade 3/4 Post-Baseline Laboratory Toxicity (Hematology and Chemistry) |
|-----------------|--|

End point description:

Laboratory parameters included hematological and chemistry parameters. Chemistry parameters included alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, calcium, creatine kinase, creatinine, glucose, magnesium, phosphate, potassium and sodium. Hematology parameters included haemoglobin, leukocytes, lymphocytes, neutrophils and platelet. Test abnormalities were graded by NCI CTCAE version 4.03 as Grade 3= severe and Grade 4= life-threatening or disabling. Only categories with at least 1 subject with abnormality are reported in this endpoint. Safety population was defined as all randomized subjects who received at least 1 dose of study drug. Unscheduled visit was performed at any time during the study whenever necessary to assess for or follow-up on AEs, at the subject's request or if deemed necessary by the investigator.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

| End point values                 | Enzalutamide:<br>DB + OLE<br>Phase | Placebo: DB<br>Phase | Placebo (DB)<br>/Enzalutamide<br>160 mg (OLE)<br>Phase |  |
|----------------------------------|------------------------------------|----------------------|--|--|
| Subject group type               | Subject analysis set               | Subject analysis set | Subject analysis set                                   |  |
| Number of subjects analysed      | 800                                | 399                  | 50   |  |
| Units: subjects                  |                                    |                      |  |  |
| Alanine Aminotransferase: High   | 2                                  | 2                    | 1  |  |
| Albumin: Low                     | 7                                  | 3                    | 0  |  |
| Alkaline Phosphatase: High       | 102                                | 74                   | 3  |  |
| Aspartate Aminotransferase: High | 3                                  | 4                    | 1  |  |
| Bilirubin: High                  | 2                                  | 0                    | 0  |  |
| Calcium: Low                     | 14                                 | 15                   | 1  |  |
| Calcium: High                    | 1                                  | 0                    | 0  |  |
| Creatine Kinase: High            | 4                                  | 2                    | 0  |  |
| Creatinine: High                 | 0                                  | 2                    | 0  |  |
| Glucose: High                    | 17                                 | 10                   | 1  |  |
| Magnesium: Low                   | 0                                  | 1                    | 0  |  |
| Magnesium: High                  | 1                                  | 1                    | 0  |  |
| Phosphate: Low                   | 28                                 | 10                   | 2  |  |
| Potassium: Low                   | 7                                  | 4                    | 1  |  |
| Potassium: High                  | 2                                  | 3                    | 0  |  |
| Sodium: Low                      | 19                                 | 13                   | 0  |  |
| Sodium: High                     | 0                                  | 1                    | 0  |  |
| Hemoglobin: Low                  | 38                                 | 20                   | 4  |  |
| Hemoglobin: High                 | 1                                  | 0                    | 0  |  |
| Leukocytes: Low                  | 8                                  | 1                    | 1  |  |
| Lymphocytes: Low                 | 80                                 | 48                   | 5  |  |
| Neutrophils: Low                 | 10                                 | 0                    | 1  |  |
| Platelet; Low                    | 4                                  | 4                    | 0  |  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

Adverse event reporting additional description:

An event may be categorized as serious in 1 subject and non serious in another, or 1 subject may experience both serious and non serious event. All TEAEs and SAEs were collected and reported. The same event may appear as both AE and SAE. Analysis was done on safety population. Total number of deaths (all causes) included only grade 5 AEs.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

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

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Enzalutamide: DB + OLE Phase |
|-----------------------|------------------------------|

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo: DB Phase |
|-----------------------|-------------------|

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months).

|                       |   |
|-----------------------|---|
| Reporting group title | Placebo (DB) /Enzalutamide 160 mg (OLE) Phase |
|-----------------------|---|

Reporting group description:

Subjects who received placebo in DB phase, completed DB Phase and entered in optional OLE Phase, received Enzalutamide capsules 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 7.7 months).

| Serious adverse events  | Enzalutamide: DB + OLE Phase | Placebo: DB Phase  | Placebo (DB) /Enzalutamide 160 mg (OLE) Phase |
|---|------------------------------|--------------------|---|
| Total subjects affected by serious adverse events                   |                              |                    |   |
| subjects affected / exposed   | 319 / 800 (39.88%)           | 155 / 399 (38.85%) | 25 / 50 (50.00%)                              |
| number of deaths (all causes)                                       | 578                          | 321                | 21  |
| number of deaths resulting from adverse events                      |                              |                    |   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |                    |   |
| Metastatic pain   |                              |                    |   |
| subjects affected / exposed   | 18 / 800 (2.25%)             | 3 / 399 (0.75%)    | 3 / 50 (6.00%)                                |
| occurrences causally related to treatment / all                     | 0 / 22                       | 1 / 3              | 0 / 3   |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 0              | 0 / 0   |
| Cancer pain   |                              |                    |   |

|   |                  |                 |                |
|---|------------------|-----------------|----------------|
| subjects affected / exposed                     | 10 / 800 (1.25%) | 5 / 399 (1.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 5           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Metastases to central nervous system            |                  |                 |                |
| subjects affected / exposed                     | 5 / 800 (0.63%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           | 0 / 0          |
| Metastases to Bone                              |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 5 / 399 (1.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Malignant pleural effusion                      |                  |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 1 / 399 (0.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Tumour pain                                     |                  |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Acute leukaemia                                 |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| Acute monocytic leukaemia                       |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| Bone marrow tumour cell infiltration            |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Metastases to liver                             |                  |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metastases to meninges                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Neoplasm progression                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Small cell lung cancer                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Transitional cell carcinoma                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal tract adenoma                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bronchial carcinoma                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metastases to lung                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute lymphocytic leukaemia                     |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Colon cancer                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Intracranial tumour haemorrhage                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myelodysplastic syndrome                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Squamous cell carcinoma of head and neck        |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Squamous cell carcinoma of lung                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Vascular disorders                              |                 |                 |                |
| Deep vein thrombosis                            |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haematoma                                       |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lymphoedema                                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypertensive crisis                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypotension                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peripheral ischaemia                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Orthostatic hypotension                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhage                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypertension                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Surgical and medical procedures                 |                 |                 |                |
| Bladder catheter removal                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Limb operation                                  |                 |                 |                |

|  |                  |                 |                |
|--|------------------|-----------------|----------------|
| subjects affected / exposed                          | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| Pain management                                      |                  |                 |                |
| subjects affected / exposed                          | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| Cataract operation                                   |                  |                 |                |
| subjects affected / exposed                          | 0 / 800 (0.00%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| Colon polypectomy                                    |                  |                 |                |
| subjects affected / exposed                          | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| Oesophageal dilation procedure                       |                  |                 |                |
| subjects affected / exposed                          | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| Pleurodesis  |                  |                 |                |
| subjects affected / exposed                          | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| Ureteral stent insertion                             |                  |                 |                |
| subjects affected / exposed                          | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                  |                 |                |
| General physical health deterioration                |                  |                 |                |
| subjects affected / exposed                          | 22 / 800 (2.75%) | 8 / 399 (2.01%) | 3 / 50 (6.00%) |
| occurrences causally related to treatment / all      | 0 / 22           | 0 / 9           | 0 / 3          |
| deaths causally related to treatment / all           | 0 / 7            | 0 / 5           | 0 / 1          |
| Asthenia   |                  |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 4 / 800 (0.50%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5           | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pain  |                 |                 |                |
| subjects affected / exposed                     | 5 / 800 (0.63%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Fatigue   |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 2 / 399 (0.50%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pyrexia   |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 5 / 399 (1.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oedema peripheral                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Malaise   |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Chest pain                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Death   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Euthanasia                                      |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| General symptom                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Device dislocation                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Device occlusion                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Disease progression                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 2          |
| Local swelling                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Immune system disorders                         |                 |                 |                |
| Anaphylactic reaction                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Reproductive system and breast disorders        |                 |                 |                |
| Pelvic pain                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Respiratory, thoracic and mediastinal disorders |                 |                 |                |
| Pulmonary embolism                              |                 |                 |                |
| subjects affected / exposed                     | 5 / 800 (0.63%) | 4 / 399 (1.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0          |
| Pleural effusion                                |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 3 / 399 (0.75%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Chronic obstructive pulmonary disease           |                 |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Pneumothorax                                    |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Epistaxis                                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary oedema                                |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Dyspnoea  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute pulmonary oedema                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Haemoptysis                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory arrest                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hydropneumothorax                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pleuritic pain                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypoxia   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Psychiatric disorders                           |                 |                 |                |
| Confusional state                               |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Depressed mood                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hallucination                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Mental status changes                           |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Depression                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Disorientation                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Investigations                                  |                 |                 |                |
| Liver function test abnormal                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Weight decreased                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Coagulation time prolonged                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemoglobin decreased                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural complications  |                 |                 |                |
| Subdural haematoma                              |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Femur fracture                                  |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Fall  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Femoral neck fracture                           |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Fracture  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hip fracture                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lumbar vertebral fracture                       |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Patella fracture                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Post procedural haematuria                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Post-traumatic pain                             |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Radiation oesophagitis                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Soft tissue injury                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Spinal compression fracture                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hand fracture                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Thoracic vertebral fracture                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Facial bones fracture                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis radiation                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Head injury                                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Heat stroke                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pelvic fracture                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pubis fracture                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rib fracture                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Congenital, familial and genetic disorders      |                 |                 |                |
| Adenomatous polyposis coli                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |                 |                 |                |
| Cardiac failure                                 |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 2 / 399 (0.50%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Angina pectoris                                 |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Acute myocardial infarction                     |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0          |
| Cardiac failure congestive                      |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial flutter                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bradycardia                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiogenic shock                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Left ventricular failure                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Mitral valve incompetance                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ventricular fibrillation                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Arrhythmia supraventricular                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial fibrillation                             |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrioventricular block complete                 |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myocardial ischaemia                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myocardial infarction                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Acute coronary syndrome                         |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Aortic valve incompetence                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac arrest                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Spinal cord compression                         |                 |                 |                |

|   |                  |                  |                |
|---|------------------|------------------|----------------|
| subjects affected / exposed                     | 54 / 800 (6.75%) | 15 / 399 (3.76%) | 3 / 50 (6.00%) |
| occurrences causally related to treatment / all | 0 / 56           | 0 / 16           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Cauda equina syndrome                           |                  |                  |                |
| subjects affected / exposed                     | 6 / 800 (0.75%)  | 0 / 399 (0.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Nerve root compression                          |                  |                  |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 4 / 399 (1.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Syncope   |                  |                  |                |
| subjects affected / exposed                     | 5 / 800 (0.63%)  | 2 / 399 (0.50%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 2            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Cerebrovascular accident                        |                  |                  |                |
| subjects affected / exposed                     | 4 / 800 (0.50%)  | 1 / 399 (0.25%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0          |
| Hepatic encephalopathy                          |                  |                  |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 2 / 399 (0.50%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 0          |
| Dizziness                                       |                  |                  |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 1 / 399 (0.25%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Transient ischemic attack                       |                  |                  |                |
| subjects affected / exposed                     | 3 / 800 (0.38%)  | 1 / 399 (0.25%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Cerebral haemorrhage                            |                  |                  |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Convulsion                                      |                 |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%) | 0 / 399 (0.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 0           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Epiduritis                                      |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nerve compression                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Partial seizures                                |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lethargy  |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Headache  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Akathisia                                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Central nervous system lesion                   |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cranial nerve palsies multiple                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Embolic stroke                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhage intracranial                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhagic stroke                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ischaemic stroke                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Lacunar infarction                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Loss of consciousness                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lumbar radiculopathy                            |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Motor dysfunction                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pachymeningitis                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Presyncope                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Status epilepticus                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypoglossal nerve paresis                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Normal pressure hydrocephalus                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Tremor  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Trigeminal neuralgia                            |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Visual field defect                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ataxia  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Carpal tunnel syndrome                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Complex partial seizures                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cranial nerve disorder                          |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myoclonus                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Paraplegia                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Sciatica  |                 |                 |                |

|   |                  |                  |                |
|---|------------------|------------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Senile dementia                                 |                  |                  |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0          |
| Subarachnoid haemorrhage                        |                  |                  |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Thalamic infarction                             |                  |                  |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| VIIth nerve paralysis                           |                  |                  |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 1 / 399 (0.25%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Neuropathy peripheral                           |                  |                  |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 0 / 399 (0.00%)  | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Blood and lymphatic system disorders            |                  |                  |                |
| Anaemia   |                  |                  |                |
| subjects affected / exposed                     | 22 / 800 (2.75%) | 12 / 399 (3.01%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 1 / 29           | 2 / 15           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Anaemia of malignant disease                    |                  |                  |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 1 / 399 (0.25%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0          |
| Disseminated intravascular coagulation          |                  |                  |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pancytopenia                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Thrombocytopenia                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Leukocytosis                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ear and labyrinth disorders                     |                 |                 |                |
| Ear pain  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Vertigo   |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Eye disorders                                   |                 |                 |                |
| Retinal detachment                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Papilloedema                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Visual acuity reduced                           |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Visual impairment                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Eyelid bleeding                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                      |                 |                 |                |
| Vomiting  |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 8 / 399 (2.01%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 2 / 3           | 4 / 9           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nausea  |                 |                 |                |
| subjects affected / exposed                     | 5 / 800 (0.63%) | 3 / 399 (0.75%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 2 / 5           | 2 / 4           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Constipation                                    |                 |                 |                |
| subjects affected / exposed                     | 5 / 800 (0.63%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rectal haemorrhage                              |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal pain                                  |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diarrhoea                                       |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 4 / 800 (0.50%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Small intestinal obstruction                    |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Faecaloma                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal haemorrhage                    |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 1 / 399 (0.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Intestinal obstruction                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal pain lower                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Colitis   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastric ulcer haemorrhage                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal obstruction                    |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haematochezia                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Intestinal perforation                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Large intestine perforation                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pancreatitis                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Proctalgia                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Retroperitoneal haemorrhage                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Intestinal mass                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pancreatitis acute                              |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peptic ulcer                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diverticulum intestinal haemorrhagic            |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer haemorrhage                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Inguinal hernia                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Large intestinal obstruction                    |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lower gastrointestinal haemorrhage              |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Proctocolitis                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders                         |                 |                 |                |
| Bile duct obstruction                           |                 |                 |                |



|   |                  |                 |                |
|---|------------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Cholangitis                                     |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Cholelithiasis                                  |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                  |                 |                |
| Hyperhidrosis                                   |                  |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Vascular purpura                                |                  |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Renal and urinary disorders                     |                  |                 |                |
| Haematuria                                      |                  |                 |                |
| subjects affected / exposed                     | 18 / 800 (2.25%) | 5 / 399 (1.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 27           | 0 / 5           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Urinary retention                               |                  |                 |                |
| subjects affected / exposed                     | 7 / 800 (0.88%)  | 8 / 399 (2.01%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 9           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Urinary tract obstruction                       |                  |                 |                |
| subjects affected / exposed                     | 8 / 800 (1.00%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Post renal failure                              |                  |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 3 / 800 (0.38%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Renal failure                                   |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal failure acute                             |                 |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bladder perforation                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hydronephrosis                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nephrolithiasis                                 |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cystitis haemorrhagic                           |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal colic                                     |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bladder obstruction                             |                 |                 |                |

|   |                  |                 |                |
|---|------------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Dysuria   |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Obstructive uropathy                            |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Ureteric obstruction                            |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Urethral obstruction                            |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Urethral stenosis                               |                  |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Endocrine disorders                             |                  |                 |                |
| Adrenal insufficiency                           |                  |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                  |                 |                |
| Back pain                                       |                  |                 |                |
| subjects affected / exposed                     | 11 / 800 (1.38%) | 7 / 399 (1.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 8           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |

|   |                  |                 |                |
|---|------------------|-----------------|----------------|
| Bone pain                                       |                  |                 |                |
| subjects affected / exposed                     | 12 / 800 (1.50%) | 3 / 399 (0.75%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 3           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Pathological fracture                           |                  |                 |                |
| subjects affected / exposed                     | 15 / 800 (1.88%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 16           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Pain in extremity                               |                  |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%)  | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Arthralgia                                      |                  |                 |                |
| subjects affected / exposed                     | 3 / 800 (0.38%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Muscular weakness                               |                  |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Myalgia   |                  |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Osteonecrosis of jaw                            |                  |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 1 / 399 (0.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Musculoskeletal chest pain                      |                  |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Chondrocalcinosis pyrophosphate                 |                  |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Flank pain                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Intervertebral disc protrusion                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Muscle haemorrhage                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Osteoarthritis                                  |                 |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rhabdomyolysis                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Spinal column stenosis                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Osteitis  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Spinal pain                                     |                 |                 |                |

|   |                  |                 |                |
|---|------------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 800 (0.25%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Bursitis  |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                  |                 |                |
| Pneumonia                                       |                  |                 |                |
| subjects affected / exposed                     | 15 / 800 (1.88%) | 5 / 399 (1.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 1 / 15           | 0 / 5           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Urinary tract infection                         |                  |                 |                |
| subjects affected / exposed                     | 9 / 800 (1.13%)  | 5 / 399 (1.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 5           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Urosepsis                                       |                  |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0          |
| Sepsis  |                  |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0           | 0 / 0          |
| Gastroenteritis                                 |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Bronchitis                                      |                  |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%)  | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Device related infection                        |                  |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 3 / 800 (0.38%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Escherichia sepsis                              |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Lobar pneumonia                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 3           | 0 / 1           | 0 / 1          |
| Staphylococcal sepsis                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cellulitis                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Erysipelas                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lower respiratory tract infection               |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal abscess                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Chest wall abscess                              |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Clostridium difficile colitis                                 |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Cystitis  |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Extradural abscess  |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Infection   |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 1           | 0 / 0           | 0 / 0          |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Kidney infection  |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Klebsiella bacteraemia  |                 |                 |                |
| subjects affected / exposed                                   | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Parotitis   |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia bacterial                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rectal abscess                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory tract infection                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Septic Shock                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Tooth Infection                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Upper respiratory tract infection               |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Herpes zoster                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Viral pericarditis                              |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abscess jaw                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Anal abscess                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atypical mycobacterial pneumonia                |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bacteraemia                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diverticulitis                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Febrile infection                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gas gangrene                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Pleural infection                               |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia pneumococcal                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary sepsis                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Pyelonephritis acute                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                 |                |
| Dehydration                                     |                 |                 |                |
| subjects affected / exposed                     | 4 / 800 (0.50%) | 3 / 399 (0.75%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyponatraemia                                   |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 3 / 399 (0.75%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypoglycaemia                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 2 / 399 (0.50%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypercalcaemia                                  |                 |                 |                |
| subjects affected / exposed                     | 2 / 800 (0.25%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyperuricaemia                                  |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypocalcaemia                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypokalaemia                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypophosphataemia                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypovolaemia                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cachexia  |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 1 / 399 (0.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Decreased appetite                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 1 / 399 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diabetes mellitus                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 800 (0.13%) | 0 / 399 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Failure to thrive                               |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| <b>Malnutrition</b>                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Hypoalbuminaemia</b>                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 800 (0.00%) | 0 / 399 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

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

| <b>Non-serious adverse events</b>                            | Enzalutamide: DB + OLE Phase | Placebo: DB Phase  | Placebo (DB) /Enzalutamide 160 mg (OLE) Phase |
|--|------------------------------|--------------------|---|
| <b>Total subjects affected by non-serious adverse events</b> |                              |                    |   |
| subjects affected / exposed                                  | 784 / 800 (98.00%)           | 385 / 399 (96.49%) | 47 / 50 (94.00%)                              |
| <b>Vascular disorders</b>                                    |                              |                    |   |
| Hot flush  |                              |                    |   |
| subjects affected / exposed                                  | 165 / 800 (20.63%)           | 41 / 399 (10.28%)  | 1 / 50 (2.00%)                                |
| occurrences (all)  | 186                          | 46                 | 1   |
| Hypertension   |                              |                    |   |
| subjects affected / exposed                                  | 60 / 800 (7.50%)             | 11 / 399 (2.76%)   | 2 / 50 (4.00%)                                |
| occurrences (all)  | 88                           | 12                 | 2   |
| <b>General disorders and administration site conditions</b>  |                              |                    |   |
| Fatigue  |                              |                    |   |
| subjects affected / exposed                                  | 280 / 800 (35.00%)           | 115 / 399 (28.82%) | 14 / 50 (28.00%)                              |
| occurrences (all)  | 424                          | 158                | 20  |
| Asthenia   |                              |                    |   |
| subjects affected / exposed                                  | 148 / 800 (18.50%)           | 67 / 399 (16.79%)  | 9 / 50 (18.00%)                               |
| occurrences (all)  | 228                          | 93                 | 11  |
| Oedema peripheral  |                              |                    |   |
| subjects affected / exposed                                  | 121 / 800 (15.13%)           | 46 / 399 (11.53%)  | 4 / 50 (8.00%)                                |
| occurrences (all)  | 145                          | 57                 | 6   |

|   |                           |                         |                      |
|---|---------------------------|-------------------------|----------------------|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 59 / 800 (7.38%)<br>70    | 23 / 399 (5.76%)<br>31  | 4 / 50 (8.00%)<br>4  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 27 / 800 (3.38%)<br>33    | 12 / 399 (3.01%)<br>16  | 3 / 50 (6.00%)<br>4  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | 88 / 800 (11.00%)<br>108  | 39 / 399 (9.77%)<br>45  | 6 / 50 (12.00%)<br>6 |
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 60 / 800 (7.50%)<br>64    | 25 / 399 (6.27%)<br>27  | 2 / 50 (4.00%)<br>2  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                           | 71 / 800 (8.88%)<br>78    | 24 / 399 (6.02%)<br>25  | 2 / 50 (4.00%)<br>2  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 55 / 800 (6.88%)<br>64    | 16 / 399 (4.01%)<br>16  | 6 / 50 (12.00%)<br>6 |
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 51 / 800 (6.38%)<br>54    | 19 / 399 (4.76%)<br>21  | 4 / 50 (8.00%)<br>4  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)   | 23 / 800 (2.88%)<br>27    | 9 / 399 (2.26%)<br>9    | 3 / 50 (6.00%)<br>4  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                          | 108 / 800 (13.50%)<br>138 | 42 / 399 (10.53%)<br>49 | 7 / 50 (14.00%)<br>8 |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)      | 44 / 800 (5.50%)<br>52    | 5 / 399 (1.25%)<br>5    | 5 / 50 (10.00%)<br>5 |
| Nervous system disorders  |                           |                         |                      |

|                                      |                    |                    |                  |
|--------------------------------------|--------------------|--------------------|------------------|
| Headache                             |                    |                    |                  |
| subjects affected / exposed          | 101 / 800 (12.63%) | 21 / 399 (5.26%)   | 1 / 50 (2.00%)   |
| occurrences (all)                    | 130                | 25                 | 1                |
| Dizziness                            |                    |                    |                  |
| subjects affected / exposed          | 59 / 800 (7.38%)   | 22 / 399 (5.51%)   | 4 / 50 (8.00%)   |
| occurrences (all)                    | 70                 | 22                 | 5                |
| Paraesthesia                         |                    |                    |                  |
| subjects affected / exposed          | 53 / 800 (6.63%)   | 18 / 399 (4.51%)   | 1 / 50 (2.00%)   |
| occurrences (all)                    | 62                 | 19                 | 1                |
| Hypoaesthesia                        |                    |                    |                  |
| subjects affected / exposed          | 33 / 800 (4.13%)   | 7 / 399 (1.75%)    | 4 / 50 (8.00%)   |
| occurrences (all)                    | 42                 | 7                  | 6                |
| Blood and lymphatic system disorders |                    |                    |                  |
| Anaemia                              |                    |                    |                  |
| subjects affected / exposed          | 123 / 800 (15.38%) | 70 / 399 (17.54%)  | 11 / 50 (22.00%) |
| occurrences (all)                    | 211                | 117                | 41               |
| Gastrointestinal disorders           |                    |                    |                  |
| Nausea                               |                    |                    |                  |
| subjects affected / exposed          | 276 / 800 (34.50%) | 166 / 399 (41.60%) | 16 / 50 (32.00%) |
| occurrences (all)                    | 391                | 218                | 19               |
| Constipation                         |                    |                    |                  |
| subjects affected / exposed          | 209 / 800 (26.13%) | 109 / 399 (27.32%) | 7 / 50 (14.00%)  |
| occurrences (all)                    | 249                | 249                | 8                |
| Diarrhoea                            |                    |                    |                  |
| subjects affected / exposed          | 180 / 800 (22.50%) | 70 / 399 (17.54%)  | 9 / 50 (18.00%)  |
| occurrences (all)                    | 251                | 82                 | 11               |
| Vomiting                             |                    |                    |                  |
| subjects affected / exposed          | 141 / 800 (17.63%) | 84 / 399 (21.05%)  | 8 / 50 (16.00%)  |
| occurrences (all)                    | 214                | 112                | 8                |
| Abdominal pain                       |                    |                    |                  |
| subjects affected / exposed          | 47 / 800 (5.88%)   | 21 / 399 (5.26%)   | 2 / 50 (4.00%)   |
| occurrences (all)                    | 51                 | 23                 | 2                |
| Abdominal pain upper                 |                    |                    |                  |
| subjects affected / exposed          | 41 / 800 (5.13%)   | 13 / 399 (3.26%)   | 0 / 50 (0.00%)   |
| occurrences (all)                    | 50                 | 16                 | 0                |
| Renal and urinary disorders          |                    |                    |                  |

|   |                    |                   |                 |
|---|--------------------|-------------------|-----------------|
| Haematuria                                      |                    |                   |                 |
| subjects affected / exposed                     | 51 / 800 (6.38%)   | 14 / 399 (3.51%)  | 3 / 50 (6.00%)  |
| occurrences (all)                               | 75                 | 19                | 3               |
| Pollakiuria                                     |                    |                   |                 |
| subjects affected / exposed                     | 44 / 800 (5.50%)   | 10 / 399 (2.51%)  | 3 / 50 (6.00%)  |
| occurrences (all)                               | 48                 | 11                | 3               |
| Musculoskeletal and connective tissue disorders |                    |                   |                 |
| Back pain                                       |                    |                   |                 |
| subjects affected / exposed                     | 225 / 800 (28.13%) | 91 / 399 (22.81%) | 9 / 50 (18.00%) |
| occurrences (all)                               | 324                | 136               | 11              |
| Arthralgia                                      |                    |                   |                 |
| subjects affected / exposed                     | 182 / 800 (22.75%) | 71 / 399 (17.79%) | 2 / 50 (4.00%)  |
| occurrences (all)                               | 276                | 112               | 2               |
| Pain in extremity                               |                    |                   |                 |
| subjects affected / exposed                     | 137 / 800 (17.13%) | 62 / 399 (15.54%) | 5 / 50 (10.00%) |
| occurrences (all)                               | 198                | 97                | 6               |
| Bone pain                                       |                    |                   |                 |
| subjects affected / exposed                     | 101 / 800 (12.63%) | 61 / 399 (15.29%) | 2 / 50 (4.00%)  |
| occurrences (all)                               | 132                | 75                | 2               |
| Musculoskeletal pain                            |                    |                   |                 |
| subjects affected / exposed                     | 121 / 800 (15.13%) | 40 / 399 (10.03%) | 3 / 50 (6.00%)  |
| occurrences (all)                               | 154                | 154               | 3               |
| Musculoskeletal chest pain                      |                    |                   |                 |
| subjects affected / exposed                     | 77 / 800 (9.63%)   | 34 / 399 (8.52%)  | 2 / 50 (4.00%)  |
| occurrences (all)                               | 101                | 44                | 2               |
| Muscular weakness                               |                    |                   |                 |
| subjects affected / exposed                     | 74 / 800 (9.25%)   | 27 / 399 (6.77%)  | 1 / 50 (2.00%)  |
| occurrences (all)                               | 95                 | 34                | 1               |
| Myalgia   |                    |                   |                 |
| subjects affected / exposed                     | 56 / 800 (7.00%)   | 26 / 399 (6.52%)  | 2 / 50 (4.00%)  |
| occurrences (all)                               | 61                 | 34                | 6               |
| Neck pain                                       |                    |                   |                 |
| subjects affected / exposed                     | 34 / 800 (4.25%)   | 17 / 399 (4.26%)  | 3 / 50 (6.00%)  |
| occurrences (all)                               | 35                 | 19                | 3               |
| Infections and infestations                     |                    |                   |                 |



|   |                           |                           |                       |
|---|---------------------------|---------------------------|-----------------------|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 68 / 800 (8.50%)<br>90    | 24 / 399 (6.02%)<br>27    | 3 / 50 (6.00%)<br>3   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)         | 47 / 800 (5.88%)<br>58    | 12 / 399 (3.01%)<br>18    | 2 / 50 (4.00%)<br>2   |
| Metabolism and nutrition disorders  |                           |                           |                       |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 246 / 800 (30.75%)<br>317 | 121 / 399 (30.33%)<br>146 | 9 / 50 (18.00%)<br>10 |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)            | 31 / 800 (3.88%)<br>37    | 14 / 399 (3.51%)<br>16    | 3 / 50 (6.00%)<br>3   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 30 July 2009    | The dose for evaluation in this study was decreased from 240 mg/day to 160 mg/day to improve the risk/benefit profile of trial.   |
| 19 April 2011   | The target number of deaths needed for the final analysis of overall survival reduced from 786 events to 650 events with an interim analysis at approximately 520 events. |
| 05 January 2012 | Access was provided to MDV3100 to patients who were either actively taking MDV3100 at the time of unblinding or were originally randomized to the placebo arm.            |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The primary objectives (overall survival) of the study had been met and all subjects who had remained on study treatment have discontinued and therefore the study has been considered as completed.

Notes: