



## Clinical trial results:

### A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or Following Docetaxel-Based Therapy

#### Summary

|                          |                                                       |
|--------------------------|-------------------------------------------------------|
| EudraCT number           | 2010-018662-23                                        |
| Trial protocol           | FR EE BE SK SE FI LT NL CZ ES AT GB PT IE GR DE IT BG |
| Global end of trial date | 29 February 2016                                      |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 16 March 2017 |
| First version publication date | 16 March 2017 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | C21005 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT01193257     |
| WHO universal trial number (UTN)   | U1111-1181-8040 |

Notes:

#### Sponsors

|                              |                                                                                                     |
|------------------------------|-----------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Millennium Pharmaceuticals, Inc.                                                                    |
| Sponsor organisation address | 40 Landsdowne Street, Cambridge, MA, United States, 02139                                           |
| Public contact               | Study Manager, Millennium Pharmaceuticals, Inc., 001 866-835-2233, GlobalOncologyMedinfo@takeda.com |
| Scientific contact           | Study Manager, Millennium Pharmaceuticals, Inc., 001 866-835-2233, GlobalOncologyMedinfo@takeda.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                       | 16 August 2016   |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 February 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To determine if orteronel plus prednisone improved overall survival.

Protection of trial subjects:

Yes

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 15 November 2010 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 10 Years         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 32        |
| Country: Number of subjects enrolled | United States: 80 |
| Country: Number of subjects enrolled | Austria: 19       |
| Country: Number of subjects enrolled | Belarus: 10       |
| Country: Number of subjects enrolled | Belgium: 13       |
| Country: Number of subjects enrolled | Bulgaria: 4       |
| Country: Number of subjects enrolled | Estonia: 5        |
| Country: Number of subjects enrolled | Finland: 11       |
| Country: Number of subjects enrolled | France: 79        |
| Country: Number of subjects enrolled | Germany: 46       |
| Country: Number of subjects enrolled | Greece: 60        |
| Country: Number of subjects enrolled | Hungary: 9        |
| Country: Number of subjects enrolled | Ireland: 9        |
| Country: Number of subjects enrolled | Italy: 21         |
| Country: Number of subjects enrolled | Portugal: 16      |
| Country: Number of subjects enrolled | Romania: 12       |
| Country: Number of subjects enrolled | Croatia: 3        |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Lithuania: 31     |
| Country: Number of subjects enrolled | Netherlands: 18   |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 22             |
| Country: Number of subjects enrolled | Russian Federation: 4  |
| Country: Number of subjects enrolled | Serbia: 4              |
| Country: Number of subjects enrolled | Slovakia: 15           |
| Country: Number of subjects enrolled | Spain: 41              |
| Country: Number of subjects enrolled | Sweden: 26             |
| Country: Number of subjects enrolled | Switzerland: 3         |
| Country: Number of subjects enrolled | United Kingdom: 107    |
| Country: Number of subjects enrolled | Argentina: 9           |
| Country: Number of subjects enrolled | Australia: 94          |
| Country: Number of subjects enrolled | Brazil: 119            |
| Country: Number of subjects enrolled | Chile: 12              |
| Country: Number of subjects enrolled | China: 11              |
| Country: Number of subjects enrolled | Colombia: 4            |
| Country: Number of subjects enrolled | Israel: 14             |
| Country: Number of subjects enrolled | Japan: 50              |
| Country: Number of subjects enrolled | Mexico: 5              |
| Country: Number of subjects enrolled | New Zealand: 12        |
| Country: Number of subjects enrolled | Singapore: 2           |
| Country: Number of subjects enrolled | South Africa: 18       |
| Country: Number of subjects enrolled | Taiwan: 14             |
| Country: Number of subjects enrolled | Korea, Republic of: 33 |
| Worldwide total number of subjects   | 1099                   |
| EEA total number of subjects         | 569                    |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 303 |
| From 65 to 84 years                       | 780 |
| 85 years and over                         | 16  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects took part in the study at 260 investigative sites in North America, Europe, Argentina, Australia, Brazil, Chile, China, Colombia, Israel, Japan, Mexico, New Zealand, Singapore, South Africa, South Korea, and Taiwan from 15 November 2010 to 29 February 2016.

### Pre-assignment

Screening details:

Male subjects with a historical diagnosis of metastatic-castration resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy were enrolled in 1 of 2 treatment groups: Orteronel 400 mg + Prednisone 5 mg or Placebo + Prednisone 5 mg.

### Period 1

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

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | Placebo + Prednisone |

Arm description:

Orteronel placebo-matching tablets, orally, twice daily (BID) and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Placebo             |
| Investigational medicinal product name | Orteronel (TAK-700) |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Film-coated tablet  |
| Routes of administration               | Oral use            |

Dosage and administration details:

Orteronel placebo-matching tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Orteronel + Prednisone |
|------------------|------------------------|

Arm description:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Orteronel (TAK-700) |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Film-coated tablet  |
| Routes of administration               | Oral use            |

Dosage and administration details:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

| <b>Number of subjects in period 1</b> | Placebo +<br>Prednisone | Orteronel +<br>Prednisone |
|---------------------------------------|-------------------------|---------------------------|
| Started                               | 365                     | 734                       |
| Treated                               | 363                     | 732                       |
| Completed                             | 0                       | 0                         |
| Not completed                         | 365                     | 734                       |
| Adverse event, serious fatal          | 202                     | 391                       |
| Consent withdrawn by subject          | 26                      | 86                        |
| Unblinded due to futility             | 135                     | 251                       |
| Study termination by sponsor          | -                       | 3                         |
| Lost to follow-up                     | 2                       | 3                         |

## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Placebo + Prednisone |
|-----------------------|----------------------|

Reporting group description:

Orteronel placebo-matching tablets, orally, twice daily (BID) and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Orteronel + Prednisone |
|-----------------------|------------------------|

Reporting group description:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

| Reporting group values                             | Placebo + Prednisone | Orteronel + Prednisone | Total |
|----------------------------------------------------|----------------------|------------------------|-------|
| Number of subjects                                 | 365                  | 734                    | 1099  |
| Age categorical<br>Units: Subjects                 |                      |                        |       |
| In utero                                           | 0                    | 0                      | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                    | 0                      | 0     |
| Newborns (0-27 days)                               | 0                    | 0                      | 0     |
| Infants and toddlers (28 days-23 months)           | 0                    | 0                      | 0     |
| Children (2-11 years)                              | 0                    | 0                      | 0     |
| Adolescents (12-17 years)                          | 0                    | 0                      | 0     |
| Adults (18-64 years)                               | 103                  | 200                    | 303   |
| From 65-84 years                                   | 256                  | 524                    | 780   |
| 85 years and over                                  | 6                    | 10                     | 16    |
| Age Continuous<br>Units: years                     |                      |                        |       |
| arithmetic mean                                    | 69.4                 | 69.2                   | -     |
| standard deviation                                 | ± 7.95               | ± 7.82                 | -     |
| Gender, Male/Female<br>Units: participants         |                      |                        |       |
| Female                                             | 0                    | 0                      | 0     |
| Male                                               | 365                  | 734                    | 1099  |
| Race/Ethnicity, Customized<br>Units: Subjects      |                      |                        |       |
| American Indian or Alaska Native                   | 1                    | 4                      | 5     |
| Asian                                              | 48                   | 77                     | 125   |
| Black or African American                          | 9                    | 18                     | 27    |
| White                                              | 305                  | 620                    | 925   |
| Unknown or Not Reported                            | 1                    | 3                      | 4     |
| Other                                              | 1                    | 12                     | 13    |
| Ethnicity (NIH/OMB)<br>Units: Subjects             |                      |                        |       |
| Hispanic or Latino                                 | 45                   | 107                    | 152   |
| Not Hispanic or Latino                             | 302                  | 588                    | 890   |
| Unknown or Not Reported                            | 18                   | 39                     | 57    |

|                                                                          |         |         |     |
|--------------------------------------------------------------------------|---------|---------|-----|
| Region of Enrollment                                                     |         |         |     |
| Units: Subjects                                                          |         |         |     |
| Canada                                                                   | 11      | 21      | 32  |
| United States                                                            | 26      | 54      | 80  |
| Austria                                                                  | 5       | 14      | 19  |
| Belarus                                                                  | 6       | 4       | 10  |
| Belgium                                                                  | 1       | 12      | 13  |
| Bulgaria                                                                 | 1       | 3       | 4   |
| Estonia                                                                  | 3       | 2       | 5   |
| Finland                                                                  | 4       | 7       | 11  |
| France                                                                   | 35      | 44      | 79  |
| Germany                                                                  | 11      | 35      | 46  |
| Greece                                                                   | 22      | 38      | 60  |
| Hungary                                                                  | 2       | 7       | 9   |
| Ireland                                                                  | 3       | 6       | 9   |
| Italy                                                                    | 7       | 14      | 21  |
| Portugal                                                                 | 8       | 8       | 16  |
| Romania                                                                  | 0       | 12      | 12  |
| Croatia                                                                  | 0       | 3       | 3   |
| Czech Republic                                                           | 1       | 1       | 2   |
| Lithuania                                                                | 9       | 22      | 31  |
| Netherlands                                                              | 6       | 12      | 18  |
| Poland                                                                   | 5       | 17      | 22  |
| Russia                                                                   | 2       | 2       | 4   |
| Serbia                                                                   | 1       | 3       | 4   |
| Slovakia                                                                 | 5       | 10      | 15  |
| Spain                                                                    | 16      | 25      | 41  |
| Sweden                                                                   | 10      | 16      | 26  |
| Switzerland                                                              | 1       | 2       | 3   |
| United Kingdom                                                           | 32      | 75      | 107 |
| Argentina                                                                | 1       | 8       | 9   |
| Australia                                                                | 28      | 66      | 94  |
| Brazil                                                                   | 37      | 82      | 119 |
| Chile                                                                    | 5       | 7       | 12  |
| China                                                                    | 5       | 6       | 11  |
| Colombia                                                                 | 0       | 4       | 4   |
| Israel                                                                   | 5       | 9       | 14  |
| Japan                                                                    | 17      | 33      | 50  |
| Mexico                                                                   | 1       | 4       | 5   |
| New Zealand                                                              | 6       | 6       | 12  |
| Singapore                                                                | 1       | 1       | 2   |
| South Africa                                                             | 4       | 14      | 18  |
| Taiwan, Province Of China                                                | 7       | 7       | 14  |
| Korea, Republic Of                                                       | 15      | 18      | 33  |
| Study Specific Characteristic   Height                                   |         |         |     |
| Height data was available for 1096 participants as follows: n= 364, 732. |         |         |     |
| Units: centimeter (cm)                                                   |         |         |     |
| arithmetic mean                                                          | 171.33  | 172.52  |     |
| standard deviation                                                       | ± 7.675 | ± 7.156 | -   |
| Study Specific Characteristic   Weight                                   |         |         |     |
| Weight data was available for 1098 participants as follows: n= 365, 733. |         |         |     |
| Units: kilogram (kg)                                                     |         |         |     |

|                                                                       |          |        |   |
|-----------------------------------------------------------------------|----------|--------|---|
| arithmetic mean                                                       | 79.85    | 82.77  |   |
| standard deviation                                                    | ± 15.183 | ± 15.2 | - |
| Study Specific Characteristic   Body mass index (BMI)                 |          |        |   |
| BMI data was available for 1095 participants as follows: n= 364, 731. |          |        |   |
| Units: kilogram per square meter (kg/m <sup>2</sup> )                 |          |        |   |
| arithmetic mean                                                       | 27.14    | 27.73  |   |
| standard deviation                                                    | ± 4.491  | ± 4.37 | - |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                       |                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                 | Placebo + Prednisone   |
| Reporting group description:<br>Orteronel placebo-matching tablets, orally, twice daily (BID) and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.                                                                                                                                                                    |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                 | Orteronel + Prednisone |
| Reporting group description:<br>Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. |                        |

### Primary: Overall Survival

|                                                                                                                                                                                                                                                                                                                                                                                                                                  |                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                  | Overall Survival |
| End point description:<br>Overall survival was calculated from the date of participant randomization to the date of participant death due to any cause. Participants without documentation of death at time of the analysis were censored as of the date the participant was last known to be alive, or the data cutoff date, whichever was earlier. Intent-to-treat (ITT) population included all subjects who were randomized. |                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                   | Primary          |
| End point timeframe:<br>Baseline until death (approximately up to 4.5 years)                                                                                                                                                                                                                                                                                                                                                     |                  |

| End point values                 | Placebo + Prednisone  | Orteronel + Prednisone |  |  |
|----------------------------------|-----------------------|------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group        |  |  |
| Number of subjects analysed      | 365                   | 734                    |  |  |
| Units: months                    |                       |                        |  |  |
| median (confidence interval 95%) | 15.3 (13.48 to 16.86) | 17.1 (15.45 to 18.67)  |  |  |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo and Orteronel                         |
| Statistical analysis description:<br>Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors region (North America, Europe and Rest of World) and brief pain inventory-short form (BPI-SF) worst pain score at screening ([less than or equal to] ≤4, greater than [>] 4) with treatment as a factor in the model. A hazard ratio less than 1 for the treatment indicates better prevention of the death in the Orteronel arm as compared to placebo arm. |                                               |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Placebo + Prednisone v Orteronel + Prednisone |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 1099              |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | equivalence       |
| P-value                                 | = 0.12085         |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.875             |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.739             |
| upper limit                             | 1.036             |

## Secondary: Radiographic Progression-free Survival (rPFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Radiographic Progression-free Survival (rPFS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                               |
| <p>rPFS was defined as the time from randomization until radiographic disease progression or death due to any cause, whichever occurred first. Radiographic disease progression was defined as the occurrence of 1 or more of the following: The appearance of 2 or more new lesions on radionuclide bone scan as defined by prostate cancer working group (PCWG)2; Should 2 or more new bone lesions be evident at the first assessment (8-week assessment) on treatment, 2 or more additional new lesions must have been evident on a confirmatory assessment at least 6 weeks later; One or more new soft tissue/visceral organ lesions identified by computed tomography (CT)/magnetic resonance imaging (MRI); Progression as defined by response evaluation criteria in solid tumors (RECIST) 1.1 criteria. ITT population included all subjects who were randomized.</p> |                                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                               |
| Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                               |

| End point values                 | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|----------------------------------|----------------------|------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed      | 365                  | 734                    |  |  |
| Units: months                    |                      |                        |  |  |
| median (confidence interval 95%) | 5.7 (5.46 to 6.97)   | 8.3 (7.76 to 8.48)     |  |  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                              | Placebo and Orteronel                         |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                       |                                               |
| <p>Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors region (North America, Europe and Rest of World) and BPI-SF worst pain score at screening (<math>\leq 4</math>, <math>&gt;4</math>) with treatment as a factor in the model. A hazard ratio less than 1 for the treatment indicates better prevention of the death in the Orteronel arm as compared to placebo arm.</p> |                                               |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                       | Placebo + Prednisone v Orteronel + Prednisone |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 1099              |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | equivalence       |
| P-value                                 | = 0.00038         |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.76              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.653             |
| upper limit                             | 0.885             |

### Secondary: Percentage of Subjects Achieving 50 Percent Reduction From Baseline in Prostate Specific Antigen (PSA50 Response) at Week 12

|                        |                                                                                                                                                                               |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Percentage of Subjects Achieving 50 Percent Reduction From Baseline in Prostate Specific Antigen (PSA50 Response) at Week 12                                                  |
| End point description: | The PSA50 was defined as the percentage of subjects who had a PSA decline of at least 50 percent (%) from baseline. ITT population included all subjects who were randomized. |
| End point type         | Secondary                                                                                                                                                                     |
| End point timeframe:   | Week 12                                                                                                                                                                       |

| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 365                  | 734                    |  |  |
| Units: percentage of subjects |                      |                        |  |  |
| number (not applicable)       | 9.9                  | 24.9                   |  |  |

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| Statistical analysis title              | Placebo and Orteronel                         |
| Statistical analysis description:       | P-values test for odds ratio equal to 1.      |
| Comparison groups                       | Placebo + Prednisone v Orteronel + Prednisone |
| Number of subjects included in analysis | 1099                                          |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | equivalence                                   |
| P-value                                 | = 0.0001                                      |
| Method                                  | Regression, Logistic                          |

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**Secondary: Percentage of Subjects With Pain Response at Week 12**

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|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Percentage of Subjects With Pain Response at Week 12 |
|-----------------|------------------------------------------------------|

End point description:

The pain response rate was calculated as the number of subjects with response divided by the number of ITT subjects in each treatment group (including those with missing data) times 100. ITT population included all subjects who were randomized.

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

End point timeframe:

Week 12

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| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 365                  | 734                    |  |  |
| Units: percentage of subjects |                      |                        |  |  |
| number (not applicable)       | 9                    | 12.1                   |  |  |

**Statistical analyses**

|                            |                       |
|----------------------------|-----------------------|
| Statistical analysis title | Placebo and Orteronel |
|----------------------------|-----------------------|

Statistical analysis description:

P-values test for odds ratio equal to 1.

|                   |                                               |
|-------------------|-----------------------------------------------|
| Comparison groups | Placebo + Prednisone v Orteronel + Prednisone |
|-------------------|-----------------------------------------------|

|                                         |      |
|-----------------------------------------|------|
| Number of subjects included in analysis | 1099 |
|-----------------------------------------|------|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | equivalence |
|---------------|-------------|

|         |           |
|---------|-----------|
| P-value | = 0.12778 |
|---------|-----------|

|        |                      |
|--------|----------------------|
| Method | Regression, Logistic |
|--------|----------------------|

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**Secondary: Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs)**

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|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs) |
|-----------------|------------------------------------------------------------------------------------|

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

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

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 59 Day 58)

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| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 363                  | 732                    |  |  |
| Units: subjects             | 345                  | 719                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Abnormal Physical Examination Findings

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Number of Subjects With Abnormal Physical Examination Findings |
|-----------------|----------------------------------------------------------------|

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

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

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 59 Day 58)

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 363                  | 732                    |  |  |
| Units: subjects             | 0                    | 1                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With TEAEs Related to Vital Signs

|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Number of Subjects With TEAEs Related to Vital Signs |
|-----------------|------------------------------------------------------|

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

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

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 59 Day 58)

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 363                  | 732                    |  |  |
| Units: subjects             |                      |                        |  |  |
| Hypertension                | 21                   | 83                     |  |  |
| Hypotension                 | 8                    | 31                     |  |  |
| Pyrexia                     | 18                   | 51                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With TEAEs Related to Weight

|                                                                                                                   |                                                 |
|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| End point title                                                                                                   | Number of Subjects With TEAEs Related to Weight |
| End point description:<br>Safety population included all subjects who received at least 1 dose of any study drug. |                                                 |
| End point type                                                                                                    | Secondary                                       |
| End point timeframe:<br>Baseline up to 30 days after last dose of study drug (Cycle 59 Day 58)                    |                                                 |

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 363                  | 732                    |  |  |
| Units: subjects             |                      |                        |  |  |
| Weight decreased            | 32                   | 107                    |  |  |
| Weight increased            | 7                    | 6                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subject With Worst Change From Baseline in Eastern Co-operative Oncology Group (ECOG) Performance Status

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Number of Subject With Worst Change From Baseline in Eastern Co-operative Oncology Group (ECOG) Performance Status |
| End point description:<br>ECOG assessed participant's performance status on 5 point scale: 0=Fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, ambulatory/able to carry out light or sedentary work; 2=ambulatory ([greater than]>50% of waking hrs), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hrs; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead. Safety population where baseline and post-baseline assessments were available. Safety population included all subjects who received at least 1 dose of any study drug. |                                                                                                                    |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                                                                                                          |

End point timeframe:

Baseline up to End-of-treatment (EOT) (Cycle 59 Day 58)

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 353                  | 705                    |  |  |
| Units: subjects             |                      |                        |  |  |
| Baseline: 0; Overall: 0     | 56                   | 112                    |  |  |
| Baseline: 0; Overall: 1     | 70                   | 121                    |  |  |
| Baseline: 0; Overall: 2     | 13                   | 47                     |  |  |
| Baseline: 0; Overall: 3     | 5                    | 18                     |  |  |
| Baseline: 0; Overall: 4     | 1                    | 3                      |  |  |
| Baseline: 1; Overall: 0     | 3                    | 10                     |  |  |
| Baseline: 1; Overall: 1     | 103                  | 179                    |  |  |
| Baseline: 1; Overall: 2     | 53                   | 113                    |  |  |
| Baseline: 1; Overall: 3     | 22                   | 39                     |  |  |
| Baseline: 1; Overall: 4     | 7                    | 11                     |  |  |
| Baseline: 2; Overall: 1     | 0                    | 6                      |  |  |
| Baseline: 2; Overall: 2     | 10                   | 25                     |  |  |
| Baseline: 2; Overall: 3     | 10                   | 18                     |  |  |
| Baseline: 2; Overall: 4     | 0                    | 3                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG)

|                                                                                         |                                                                                 |
|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| End point title                                                                         | Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) |
| End point description:                                                                  |                                                                                 |
| Safety population included all subjects who received at least 1 dose of any study drug. |                                                                                 |
| End point type                                                                          | Secondary                                                                       |
| End point timeframe:                                                                    |                                                                                 |
| Cycle 59 Day 58                                                                         |                                                                                 |

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 363                  | 732                    |  |  |
| Units: subjects             | 1                    | 3                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With TEAEs Categorized Into Investigations Related to Chemistry, Hematology or Steroid Hormone Panel

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With TEAEs Categorized Into Investigations Related to Chemistry, Hematology or Steroid Hormone Panel |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

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

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 59 Day 58)

| End point values                                   | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|----------------------------------------------------|----------------------|------------------------|--|--|
| Subject group type                                 | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed                        | 363                  | 732                    |  |  |
| Units: subjects                                    |                      |                        |  |  |
| number (not applicable)                            |                      |                        |  |  |
| Digestive enzymes                                  | 9                    | 140                    |  |  |
| Renal function analyses                            | 13                   | 41                     |  |  |
| Liver function analyses                            | 14                   | 38                     |  |  |
| Tissue enzyme analyses NEC                         | 16                   | 30                     |  |  |
| Coagulation and bleeding analyses                  | 1                    | 17                     |  |  |
| Mineral and electrolyte analyses                   | 5                    | 9                      |  |  |
| White blood cell analyses                          | 4                    | 8                      |  |  |
| Carbohydrate tolerance analyses(includingdiabetes) | 0                    | 8                      |  |  |
| Urinary tract function analyses NEC                | 1                    | 5                      |  |  |
| Platelet analyses                                  | 3                    | 4                      |  |  |
| Cholesterol analyses                               | 1                    | 4                      |  |  |
| Red blood cell analyses                            | 2                    | 3                      |  |  |
| Protein analyses not else where classified (NEC)   | 0                    | 3                      |  |  |
| Vascular tests NEC (including blood pressure)      | 3                    | 2                      |  |  |
| Adrenal cortex tests                               | 0                    | 2                      |  |  |
| Metabolism tests NEC                               | 0                    | 2                      |  |  |
| Skeletal and cardiac muscle analyses               | 0                    | 2                      |  |  |
| Triglyceride analyses                              | 0                    | 1                      |  |  |
| Urinalysis NEC                                     | 0                    | 1                      |  |  |
| Vitamin analyses                                   | 0                    | 1                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving PSA50 Response at any Time During the Study

|                 |                                                                              |
|-----------------|------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Achieving PSA50 Response at any Time During the Study |
|-----------------|------------------------------------------------------------------------------|

End point description:

The PSA50 was defined as the percentage of subjects who had a PSA decline of at least 50% from baseline. ITT population where baseline and post-baseline assessments were available. The ITT population included all subjects who were randomized.

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

End point timeframe:

Cycle: 4, 7, 10, 13, 16, 19, 22, and 25

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 365                  | 734                    |  |  |
| Units: subjects             |                      |                        |  |  |
| number (not applicable)     |                      |                        |  |  |
| Cycle 4 (n= 283; 559)       | 12.72                | 32.74                  |  |  |
| Cycle 7 (n= 163; 403)       | 18.4                 | 38.21                  |  |  |
| Cycle 10 (n= 102; 267)      | 22.55                | 36.7                   |  |  |
| Cycle 13 (n= 55; 171)       | 23.64                | 40.94                  |  |  |
| Cycle 16 (n= 34; 107)       | 23.53                | 44.86                  |  |  |
| Cycle 19 (n= 24; 68)        | 20.83                | 42.65                  |  |  |
| Cycle 22 (n= 14; 36)        | 28.57                | 52.78                  |  |  |
| Cycle 25 (n= 8; 16)         | 25                   | 62.5                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving 90 Percent Reduction From Baseline in Prostate Specific Antigen (PSA90 Response) at Week 12

|                 |                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Achieving 90 Percent Reduction From Baseline in Prostate Specific Antigen (PSA90 Response) at Week 12 |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|

End point description:

The PSA90 was defined as the percentage of subjects who had a PSA decline of at least 90% from

baseline. ITT population included all subjects who were randomized.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 283                  | 559                    |  |  |
| Units: percentage of subjects |                      |                        |  |  |
| number (not applicable)       | 2.83                 | 9.66                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving PSA90 Response at any Time During the Study

|                 |                                                                              |
|-----------------|------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Achieving PSA90 Response at any Time During the Study |
|-----------------|------------------------------------------------------------------------------|

End point description:

The PSA90 was defined as the percentage of subjects who had a PSA decline of at least 90% from baseline. ITT population where baseline and post-baseline assessments were available. ITT population included all subjects who were randomized.

|                                      |           |
|--------------------------------------|-----------|
| End point type                       | Secondary |
| End point timeframe:                 |           |
| Cycle: 7, 10, 13, 16, 19, 22, and 25 |           |

| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 365                  | 734                    |  |  |
| Units: percentage of subjects |                      |                        |  |  |
| number (not applicable)       |                      |                        |  |  |
| Cycle 7 (n=163; 403)          | 4.91                 | 14.89                  |  |  |
| Cycle 10 (n=102; 267)         | 6.86                 | 14.23                  |  |  |
| Cycle 13 (n=55; 171)          | 7.27                 | 15.2                   |  |  |
| Cycle 16 (n=34; 107)          | 5.88                 | 19.63                  |  |  |
| Cycle 19 (n=24; 68)           | 4.17                 | 23.53                  |  |  |
| Cycle 22 (n=14; 36)           | 0                    | 27.78                  |  |  |
| Cycle 25 (n=8; 16)            | 0                    | 43.75                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Best PSA Response at any Time During the Study

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Best PSA Response at any Time During the Study |
|-----------------|------------------------------------------------|

End point description:

The PSA50 was defined as the percentage of subjects who had a PSA decline of at least 50% from baseline. PSA90 was defined as the percentage of subjects who had a PSA decline of at least 90% from baseline.

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

End point timeframe:

Cycle: 4, 7, 10, 13, 16, 19, 22, and 25

| End point values                     | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed          | 0 <sup>[1]</sup>     | 0 <sup>[2]</sup>       |  |  |
| Units: ng/mL                         |                      |                        |  |  |
| arithmetic mean (standard deviation) | ( )                  | ( )                    |  |  |

Notes:

[1] - Best PSA response was not evaluated due to change in planned analysis.

[2] - Best PSA response was not evaluated due to change in planned analysis.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to PSA Progression

|                 |                         |
|-----------------|-------------------------|
| End point title | Time to PSA Progression |
|-----------------|-------------------------|

End point description:

Time to PSA progression was defined as time from randomization to 25% and 2 nanogram per milliliter (ng/mL) or greater increase in PSA above the baseline assessment (if no PSA decline from the baseline assessment). ITT population included all subjects who were randomized.

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

End point timeframe:

Baseline until the final on treatment assessment or until end of short term follow-up following discontinuation of treatment, whichever occurred later (approximately up to 4.5 years)

| End point values                 | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|----------------------------------|----------------------|------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed      | 365                  | 734                    |  |  |
| Units: months                    |                      |                        |  |  |
| median (confidence interval 95%) | 2.9 (2.83 to 2.9)    | 5.5 (4.4 to 5.56)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Shifts From Baseline Between Favorable and Unfavorable Categories in Circulating Tumor Cell Count (CTC)

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Shifts From Baseline Between Favorable and Unfavorable Categories in Circulating Tumor Cell Count (CTC) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

A favorable CTC count was defined as less than (<) 5 counts per (/) 7.5 milliliter (mL) in whole blood. An unfavorable CTC count was defined as greater than or equal to ( $\geq$ ) 5 counts/7.5 mL in whole blood. ITT population where baseline and post-baseline assessments were available. ITT population included all subjects who were randomized.

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

End point timeframe:

Baseline and EOT (Cycle 59 Day 58)

| End point values                        | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------------------|----------------------|------------------------|--|--|
| Subject group type                      | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed             | 365                  | 734                    |  |  |
| Units: subjects                         |                      |                        |  |  |
| Baseline: Favorable; EOT: Favorable     | 27                   | 63                     |  |  |
| Baseline: Favorable; EOT: Unfavorable   | 30                   | 40                     |  |  |
| Baseline: Unfavorable; EOT: Favorable   | 8                    | 23                     |  |  |
| Baseline: Unfavorable; EOT: Unfavorable | 92                   | 141                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Objective Response

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Percentage of Subjects with Objective Response |
|-----------------|------------------------------------------------|

End point description:

Percentage of subjects with objective response based assessment of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1. The overall objective response was defined as a CR or PR. A CR was defined as the disappearance of all target lesions determined by computerized tomography (CT) or MRI. Any pathological lymph nodes (whether target or non-target) must have had reduction in short axis to <10 millimetre (mm). A PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of longest diameters of non-lymph node lesions and of the short diameter(s) or short axis of lymph nodes. Response per RECIST-evaluable population was defined as a subset of subjects who had measurable disease by RECIST 1.1 at baseline.

|                                                                                                       |           |
|-------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                        | Secondary |
| End point timeframe:                                                                                  |           |
| Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years) |           |

| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 146                  | 280                    |  |  |
| Units: percentage of subjects |                      |                        |  |  |
| number (not applicable)       | 2.7                  | 17.1                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Pain Progression

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Time to Pain Progression |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                          |
| Time to pain progression was defined as the time from subject randomization to the first assessment date of pain progression. Pain progression was defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: The brief pain inventory-short form (BPI-SF) worst pain score was $\geq 4$ with a $\geq 2$ point increase over baseline in BPI-SF worst pain score with stable or increased analgesic use; The BPI-SF worst pain score was $\geq 4$ but not less than baseline with new or increased (relative to baseline) Step II or Step III analgesic use; The BPI-SF worst pain score was $\leq 3$ but not less than baseline with new or increased (relative to baseline) Step III analgesic use. ITT population included all subjects who were randomized. For Placebo + Prednisone arm, 99999 is mentioned for upper limit of CI because the upper limit of CI was not estimable for this arm. |                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          |
| Baseline until EOT visit or until end of short term follow-up, whichever occurred later (approximately up to 4.5 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                          |

| End point values                 | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|----------------------------------|----------------------|------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed      | 365                  | 734                    |  |  |
| Units: months                    |                      |                        |  |  |
| median (confidence interval 95%) | 22 (20.48 to 99999)  | 24.2 (18.24 to 24.2)   |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Pain Response

|                 |                       |
|-----------------|-----------------------|
| End point title | Time to Pain Response |
|-----------------|-----------------------|

End point description:

Time to pain response was defined as the time from randomization until first pain response. Pain response was defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: A  $\geq 2$  point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use, or a 25% or more reduction in analgesic use from baseline without an increase in worst pain score from baseline.

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

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)

| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 0 <sup>[3]</sup>     | 0 <sup>[4]</sup>       |  |  |
| Units: months                 |                      |                        |  |  |
| median (full range (min-max)) | ( to )               | ( to )                 |  |  |

Notes:

[3] - No data reported, median time to pain response was not estimable, not reached in any treatment group.

[4] - No data reported, median time to pain response was not estimable, not reached in any treatment group.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Best Pain Response

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Number of Subjects with Best Pain Response |
|-----------------|--------------------------------------------|

End point description:

Best pain response was evaluated in subjects who had a pain response across the entire study were summarized by treatment group. The pain response was defined as a  $\geq 2$ -point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use, or a 25% or more reduction in analgesic use from baseline without an increase in worst pain score from baseline. ITT population included all subjects who were randomized.

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

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)

| End point values            | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 365                  | 734                    |  |  |
| Units: subjects             | 72                   | 166                    |  |  |

## Statistical analyses

## Secondary: Percentage of Subjects with Health-related Quality of Life (HRQOL) Response at Week 12

|                 |                                                                                        |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Health-related Quality of Life (HRQOL) Response at Week 12 |
|-----------------|----------------------------------------------------------------------------------------|

### End point description:

The Global health status or quality of life(QOL) was measured as HRQOL response rate at 12 weeks using 2-item global health status index of european organization for research and treatment of cancer-quality of life questionnaire-C30 (EORTC QLQ-C30) instrument. HRQOL response was defined as 17-point increase from baseline assessment on QOL index, after score had been linearly transformed to 0 to 100 scale. EORTC QLQ-C30: included 5 functional scales(physical, role, cognitive, emotional, and social),1 global health status,3 symptom scales (fatigue, pain, nausea/vomiting) and 6 single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea and financial difficulties). Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores averaged, transformed to 0-100 scale; higher score showed better level of functioning or greater degree of symptoms. ITT population included all subjects who were randomized.

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

### End point timeframe:

Week 12

| End point values              | Placebo + Prednisone | Orteronel + Prednisone |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed   | 365                  | 734                    |  |  |
| Units: percentage of subjects |                      |                        |  |  |
| number (not applicable)       | 9.9                  | 8.7                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days after the last dose of study drug.

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

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

### Dictionary used

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

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

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Orteronel + Prednisone |
|-----------------------|------------------------|

Reporting group description:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Placebo + Prednisone |
|-----------------------|----------------------|

Reporting group description:

Orteronel placebo-matching tablets, orally, twice daily (BID) and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

| Serious adverse events                                              | Orteronel + Prednisone | Placebo + Prednisone |  |
|---------------------------------------------------------------------|------------------------|----------------------|--|
| Total subjects affected by serious adverse events                   |                        |                      |  |
| subjects affected / exposed                                         | 384 / 732 (52.46%)     | 148 / 363 (40.77%)   |  |
| number of deaths (all causes)                                       | 85                     | 48                   |  |
| number of deaths resulting from adverse events                      | 0                      | 1                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                      |  |
| Prostate cancer                                                     |                        |                      |  |
| subjects affected / exposed                                         | 33 / 732 (4.51%)       | 24 / 363 (6.61%)     |  |
| occurrences causally related to treatment / all                     | 0 / 42                 | 0 / 29               |  |
| deaths causally related to treatment / all                          | 0 / 20                 | 0 / 20               |  |
| Prostate cancer metastatic                                          |                        |                      |  |
| subjects affected / exposed                                         | 6 / 732 (0.82%)        | 4 / 363 (1.10%)      |  |
| occurrences causally related to treatment / all                     | 0 / 7                  | 0 / 5                |  |
| deaths causally related to treatment / all                          | 0 / 5                  | 0 / 4                |  |
| Metastatic pain                                                     |                        |                      |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 9 / 732 (1.23%) | 5 / 363 (1.38%) |  |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cancer pain                                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour pain                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic pulmonary embolism                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to meninges                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to bone                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Lymphangiosis carcinomatosa                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastases to central nervous system            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to liver                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastases to the mediastinum                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastases to lung                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to lymph nodes                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone marrow tumour cell infiltration            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal cancer recurrent                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic lymphocytic leukaemia                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic renal cell carcinoma                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder neoplasm                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neoplasm malignant                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orthostatic hypotension                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage                                     |                 |                 |  |

|                                                      |                  |                 |  |
|------------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                          | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 2            | 0 / 0           |  |
| Embolism                                             |                  |                 |  |
| subjects affected / exposed                          | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Thrombosis                                           |                  |                 |  |
| subjects affected / exposed                          | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Hypertension                                         |                  |                 |  |
| subjects affected / exposed                          | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Hypertensive crisis                                  |                  |                 |  |
| subjects affected / exposed                          | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Lymphoedema                                          |                  |                 |  |
| subjects affected / exposed                          | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 2 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Phlebitis                                            |                  |                 |  |
| subjects affected / exposed                          | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General disorders and administration site conditions |                  |                 |  |
| General physical health deterioration                |                  |                 |  |
| subjects affected / exposed                          | 19 / 732 (2.60%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all      | 2 / 24           | 2 / 6           |  |
| deaths causally related to treatment / all           | 0 / 7            | 0 / 1           |  |
| Multi-organ failure                                  |                  |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0           |  |
| Disease progression                             |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1           |  |
| Performance status decreased                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Fatigue                                         |                  |                 |  |
| subjects affected / exposed                     | 10 / 732 (1.37%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 6 / 10           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Asthenia                                        |                  |                 |  |
| subjects affected / exposed                     | 10 / 732 (1.37%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 5 / 13           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Malaise                                         |                  |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 2 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyrexia                                         |                  |                 |  |
| subjects affected / exposed                     | 8 / 732 (1.09%)  | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 2 / 8            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pain                                            |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chest pain                                      |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 732 (0.27%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised oedema                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Death                                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Thrombosis in device                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device occlusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Systemic inflammatory response syndrome         |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Drug intolerance                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gait disturbance                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cyst                                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Reproductive system and breast disorders        |                  |                 |  |
| Prostatomegaly                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pelvic pain                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                  |                 |  |
| Pulmonary embolism                              |                  |                 |  |
| subjects affected / exposed                     | 20 / 732 (2.73%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 7 / 21           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1           |  |
| Dyspnoea                                        |                  |                 |  |
| subjects affected / exposed                     | 8 / 732 (1.09%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 7 / 732 (0.96%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 2           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Alveolitis allergic                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleuritic pain                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchospasm                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary arterial hypertension                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung disorder                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 4 / 732 (0.55%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Depression                                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Delusion                                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Psychotic disorder                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Delirium                                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Investigations                                  |                  |                 |  |
| Lipase increased                                |                  |                 |  |
| subjects affected / exposed                     | 12 / 732 (1.64%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 13 / 13          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Amylase increased                               |                  |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 5 / 6            | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatic enzymes increased                    |                  |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 5 / 5            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Liver function test abnormal                    |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| International normalised ratio increased        |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood cortisol decreased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood glucose increased                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood alkaline phosphatase increased            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint dislocation                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament sprain                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Overdose                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radiation proctitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transfusion-related circulatory overload        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Kidney rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 9 / 732 (1.23%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 3 / 9           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiopulmonary failure                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Atrioventricular block complete                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Left ventricular dysfunction                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Aortic valve stenosis                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mitral valve incompetence                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cor pulmonale                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nervous system disorders                        |                  |                 |  |
| Spinal cord compression                         |                  |                 |  |
| subjects affected / exposed                     | 17 / 732 (2.32%) | 9 / 363 (2.48%) |  |
| occurrences causally related to treatment / all | 0 / 20           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cauda equina syndrome                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nerve root compression                          |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 8 / 732 (1.09%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 11          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lethargy                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebral ischaemia                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intraventricular haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central nervous system haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular encephalopathy                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertebrobasilar insufficiency                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ataxia                                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic encephalopathy                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| VIIth nerve paralysis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cognitive disorder                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parkinson's disease                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tremor                                          |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Seizure                                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neuralgia                                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood and lymphatic system disorders            |                  |                 |  |
| Anaemia                                         |                  |                 |  |
| subjects affected / exposed                     | 21 / 732 (2.87%) | 9 / 363 (2.48%) |  |
| occurrences causally related to treatment / all | 3 / 22           | 1 / 11          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombocytopenia                                |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombotic thrombocytopenic purpura             |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Disseminated intravascular coagulation          |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Anaemia of chronic disease                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anaemia of malignant disease                    |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphadenopathy                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemolytic anaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Haemolytic uraemic syndrome                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo                                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tinnitus                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertigo positional                              |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |
| Diplopia                                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Vomiting                                        |                  |                 |  |
| subjects affected / exposed                     | 18 / 732 (2.46%) | 6 / 363 (1.65%) |  |
| occurrences causally related to treatment / all | 11 / 20          | 2 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nausea                                          |                  |                 |  |
| subjects affected / exposed                     | 13 / 732 (1.78%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 9 / 14           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain                                  |                  |                 |  |
| subjects affected / exposed                     | 10 / 732 (1.37%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 2 / 13           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain upper                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain lower                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Constipation                                    |                  |                 |  |
| subjects affected / exposed                     | 6 / 732 (0.82%)  | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subileus                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ulcerative                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroduodenitis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 732 (0.00%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal haemorrhage                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal distension                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Enterocolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retroperitoneal haemorrhage                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis erosive                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis intestinal haemorrhagic          |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholestasis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice                                        |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatic function abnormal                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatic failure                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholelithiasis                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bile duct stenosis                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                  |                 |  |
| Decubitus ulcer                                 |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal and urinary disorders                     |                  |                 |  |
| Acute kidney injury                             |                  |                 |  |
| subjects affected / exposed                     | 12 / 732 (1.64%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 1 / 15           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal failure                                   |                  |                 |  |
| subjects affected / exposed                     | 11 / 732 (1.50%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 6 / 13           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0           |  |
| Postrenal failure                               |                  |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal impairment                                |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Chronic kidney disease                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urinary retention                               |                  |                 |  |
| subjects affected / exposed                     | 14 / 732 (1.91%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 15           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dysuria                                         |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urge incontinence                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Micturition urgency                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haematuria                                      |                  |                 |  |
| subjects affected / exposed                     | 9 / 732 (1.23%)  | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hydronephrosis                                  |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 732 (0.41%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstructive uropathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Azotaemia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urethral                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract obstruction                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinoma                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder perforation                             |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ureteric rupture                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Endocrine disorders                             |                  |                 |  |
| Adrenal insufficiency                           |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 3 / 3            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mineralocorticoid deficiency                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Inappropriate antidiuretic hormone secretion    |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperthyroidism                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                  |                 |  |
| Back pain                                       |                  |                 |  |
| subjects affected / exposed                     | 10 / 732 (1.37%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 1 / 10           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Musculoskeletal pain                            |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| Pain in extremity                               |                 |                  |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 2 / 363 (0.55%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Musculoskeletal chest pain                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bone pain                                       |                 |                  |  |
| subjects affected / exposed                     | 8 / 732 (1.09%) | 14 / 363 (3.86%) |  |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Spinal pain                                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pubic pain                                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pathological fracture                           |                 |                  |  |
| subjects affected / exposed                     | 7 / 732 (0.96%) | 1 / 363 (0.28%)  |  |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Osteoporotic fracture                           |                 |                  |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Arthralgia                                      |                 |                  |  |
| subjects affected / exposed                     | 4 / 732 (0.55%) | 0 / 363 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Muscular weakness                               |                 |                  |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Osteonecrosis of jaw                            |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chondrocalcinosis pyrophosphate                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Spinal column stenosis                          |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myositis                                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mobility decreased                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myopathy                                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Sepsis                                          |                  |                 |  |
| subjects affected / exposed                     | 14 / 732 (1.91%) | 3 / 363 (0.83%) |  |
| occurrences causally related to treatment / all | 1 / 17           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1           |  |
| Urosepsis                                       |                  |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 12 / 732 (1.64%) | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Septic shock                                    |                  |                 |  |
| subjects affected / exposed                     | 7 / 732 (0.96%)  | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2           |  |
| Bacteraemia                                     |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia                                       |                  |                 |  |
| subjects affected / exposed                     | 19 / 732 (2.60%) | 9 / 363 (2.48%) |  |
| occurrences causally related to treatment / all | 5 / 24           | 1 / 11          |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 1           |  |
| Lower respiratory tract infection               |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 2 / 363 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lung infection                                  |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Bronchopneumonia                                |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Lobar pneumonia                                 |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urinary tract infection                         |                  |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 20 / 732 (2.73%) | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 0 / 25           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyelonephritis                                  |                  |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyelonephritis acute                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyelonephritis chronic                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Appendicitis                                    |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastroenteritis                                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anal abscess                                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal infection                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticulitis                                  |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Rectal abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 5 / 732 (0.68%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis bacterial                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal bacteraemia                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess oral                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Soft tissue infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia pneumococcal                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fungal oesophagitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proteus infection                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Salmonella sepsis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Spinal cord infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nosocomial infection                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Listeriosis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 732 (0.00%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 15 / 732 (2.05%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 3 / 18           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperkalaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 10 / 732 (1.37%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 5 / 10           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypokalaemia                                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperglycaemia                                  |                  |                 |  |
| subjects affected / exposed                     | 10 / 732 (1.37%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 8 / 10           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Decreased appetite                              |                  |                 |  |
| subjects affected / exposed                     | 4 / 732 (0.55%)  | 4 / 363 (1.10%) |  |
| occurrences causally related to treatment / all | 2 / 4            | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypercalcaemia                                  |                  |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%)  | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypocalcaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetes mellitus                               |                  |                 |  |
| subjects affected / exposed                     | 3 / 732 (0.41%)  | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyponatraemia                                   |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 732 (0.27%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic ketoacidosis                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cachexia                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 732 (0.27%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 1 / 363 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Electrolyte imbalance                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lactic acidosis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 732 (0.14%) | 0 / 363 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | <b>Orteronel + Prednisone</b> | <b>Placebo + Prednisone</b> |  |
|-------------------------------------------------------|-------------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events |                               |                             |  |
| subjects affected / exposed                           | 703 / 732 (96.04%)            | 341 / 363 (93.94%)          |  |
| Investigations                                        |                               |                             |  |
| Weight decreased                                      |                               |                             |  |
| subjects affected / exposed                           | 113 / 732 (15.44%)            | 34 / 363 (9.37%)            |  |
| occurrences (all)                                     | 140                           | 41                          |  |
| Lipase increased                                      |                               |                             |  |

|                                                                                |                           |                         |  |
|--------------------------------------------------------------------------------|---------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                               | 113 / 732 (15.44%)<br>149 | 5 / 363 (1.38%)<br>5    |  |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)          | 101 / 732 (13.80%)<br>133 | 5 / 363 (1.38%)<br>5    |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all) | 38 / 732 (5.19%)<br>50    | 9 / 363 (2.48%)<br>11   |  |
| Vascular disorders                                                             |                           |                         |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)               | 84 / 732 (11.48%)<br>98   | 22 / 363 (6.06%)<br>23  |  |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)                  | 63 / 732 (8.61%)<br>64    | 20 / 363 (5.51%)<br>20  |  |
| Nervous system disorders                                                       |                           |                         |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                   | 76 / 732 (10.38%)<br>89   | 23 / 363 (6.34%)<br>30  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 78 / 732 (10.66%)<br>101  | 15 / 363 (4.13%)<br>16  |  |
| Blood and lymphatic system disorders                                           |                           |                         |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                    | 103 / 732 (14.07%)<br>133 | 59 / 363 (16.25%)<br>80 |  |
| General disorders and administration<br>site conditions                        |                           |                         |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                    | 223 / 732 (30.46%)<br>284 | 84 / 363 (23.14%)<br>95 |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                   | 102 / 732 (13.93%)<br>145 | 39 / 363 (10.74%)<br>44 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)          | 77 / 732 (10.52%)<br>94   | 45 / 363 (12.40%)<br>48 |  |

|                                                                    |                           |                          |  |
|--------------------------------------------------------------------|---------------------------|--------------------------|--|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)        | 48 / 732 (6.56%)<br>57    | 18 / 363 (4.96%)<br>23   |  |
| Gastrointestinal disorders                                         |                           |                          |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)         | 319 / 732 (43.58%)<br>456 | 94 / 363 (25.90%)<br>115 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)       | 272 / 732 (37.16%)<br>541 | 60 / 363 (16.53%)<br>83  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 222 / 732 (30.33%)<br>279 | 64 / 363 (17.63%)<br>74  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)      | 201 / 732 (27.46%)<br>286 | 54 / 363 (14.88%)<br>65  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 46 / 732 (6.28%)<br>57    | 21 / 363 (5.79%)<br>26   |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)      | 46 / 732 (6.28%)<br>56    | 13 / 363 (3.58%)<br>14   |  |
| Respiratory, thoracic and mediastinal disorders                    |                           |                          |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)       | 67 / 732 (9.15%)<br>80    | 21 / 363 (5.79%)<br>22   |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)          | 63 / 732 (8.61%)<br>69    | 19 / 363 (5.23%)<br>22   |  |
| Psychiatric disorders                                              |                           |                          |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)       | 67 / 732 (9.15%)<br>75    | 26 / 363 (7.16%)<br>26   |  |
| Musculoskeletal and connective tissue disorders                    |                           |                          |  |
| Back pain                                                          |                           |                          |  |

|                                    |                    |                   |  |
|------------------------------------|--------------------|-------------------|--|
| subjects affected / exposed        | 139 / 732 (18.99%) | 62 / 363 (17.08%) |  |
| occurrences (all)                  | 196                | 85                |  |
| Arthralgia                         |                    |                   |  |
| subjects affected / exposed        | 112 / 732 (15.30%) | 55 / 363 (15.15%) |  |
| occurrences (all)                  | 150                | 71                |  |
| Bone pain                          |                    |                   |  |
| subjects affected / exposed        | 89 / 732 (12.16%)  | 51 / 363 (14.05%) |  |
| occurrences (all)                  | 117                | 61                |  |
| Muscle spasms                      |                    |                   |  |
| subjects affected / exposed        | 110 / 732 (15.03%) | 27 / 363 (7.44%)  |  |
| occurrences (all)                  | 167                | 31                |  |
| Pain in extremity                  |                    |                   |  |
| subjects affected / exposed        | 86 / 732 (11.75%)  | 45 / 363 (12.40%) |  |
| occurrences (all)                  | 116                | 57                |  |
| Musculoskeletal pain               |                    |                   |  |
| subjects affected / exposed        | 57 / 732 (7.79%)   | 24 / 363 (6.61%)  |  |
| occurrences (all)                  | 73                 | 30                |  |
| Myalgia                            |                    |                   |  |
| subjects affected / exposed        | 39 / 732 (5.33%)   | 20 / 363 (5.51%)  |  |
| occurrences (all)                  | 46                 | 22                |  |
| Muscular weakness                  |                    |                   |  |
| subjects affected / exposed        | 36 / 732 (4.92%)   | 21 / 363 (5.79%)  |  |
| occurrences (all)                  | 40                 | 23                |  |
| Musculoskeletal chest pain         |                    |                   |  |
| subjects affected / exposed        | 39 / 732 (5.33%)   | 16 / 363 (4.41%)  |  |
| occurrences (all)                  | 44                 | 18                |  |
| Infections and infestations        |                    |                   |  |
| Urinary tract infection            |                    |                   |  |
| subjects affected / exposed        | 57 / 732 (7.79%)   | 24 / 363 (6.61%)  |  |
| occurrences (all)                  | 75                 | 29                |  |
| Metabolism and nutrition disorders |                    |                   |  |
| Decreased appetite                 |                    |                   |  |
| subjects affected / exposed        | 208 / 732 (28.42%) | 68 / 363 (18.73%) |  |
| occurrences (all)                  | 249                | 75                |  |
| Hypokalaemia                       |                    |                   |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 45 / 732 (6.15%) | 14 / 363 (3.86%) |  |
| occurrences (all)           | 52               | 14               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13 May 2011   | Revised minimum prior docetaxel exposure received within a 6-month period for subjects with progressive disease and that subjects must have received 1 or 2 lines or regimens of prior therapy; Eliminated washout period for discontinued prior antiandrogen therapy for subjects enrolling in study; Clarified that dose modifications applied to blinded study drug; and subjects with asymptomatic Grade 3/4 laboratory findings not related to study drug may not have required dose modification; Clarified that subjects must receive first dose of study drug within 7 days of randomization, documentation demonstrating that subject had progressive disease must have been submitted to the sponsor along with a Patient Eligibility Worksheet and information on medications being taken at time of screening was not collected; Added an early interim analysis to occur after approximately 50% of planned events; Clarified that evaluation of pain was to be performed at unscheduled visits; Updated the contact information for reporting of SAEs; Clarified the collection period for SAEs; Clarified the radiographic disease assessments according to the PCWG2 and modified RECIST; Updated safety information from ongoing clinical trials with Orteronel; Updated the PSA data from Study TAK-700_201; Provided the rationale for enumeration of CTCs; Clarified the rationale for genotyping and assessment of biomarkers in tumor tissue; Updated information on the potential risks of Orteronel. |
| 22 June 2011  | Clarified that dose modifications were required for Grade 3 or 4 AEs or intolerable Grade 2 AEs that were considered at least possibly related to study drug.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 26 March 2013 | Updated procedures for recording and reporting AEs and SAEs to be consistent with the sponsor's current procedures; Updated details on the monitoring of AEs throughout the study to be consistent with the sponsor's current procedures; Clarified that a listing of TEAEs resulting in study drug discontinuation would be provided; Updated status of ongoing clinical trials with orteronel to include Studies C21004, C21008, C21009, C21012, and C21013; Added background information on enzalutamide and abiraterone acetate to the study rationale; Updated the risk language of orteronel, per the most recent Investigator Brochure data cutoff date, 29 September 2012; Updated pancreas-related SAEs, per the most recent Investigator Brochure data cutoff date, 29 September 2012; Updated the risk language for T-1358043 (a process impurity, drug product degradant, and minor metabolite of orteronel) based on nonclinical studies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported