



## Clinical trial results:

**A randomized, double-blind, placebo-controlled Phase III study of darolutamide (ODM-201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer**

### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2015-002590-38                      |
| Trial protocol           | GB SE BE ES FI DE CZ NL PL FR BG IT |
| Global end of trial date | 11 April 2023                       |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 10 April 2024 |
| First version publication date | 10 April 2024 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY1841788/17777 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02799602 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bayer AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368                                   |
| Public contact               | Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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                       | 11 April 2023 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 11 April 2023 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the superiority in overall survival (OS) of darolutamide in addition to standard androgen deprivation therapy (ADT) and docetaxel over placebo in addition to standard ADT and docetaxel.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

ADT of the investigator's choice (luteinizing hormone-releasing hormone [LHRH] agonist/antagonist or orchiectomy) as standard therapy, started  $\leq 12$  weeks before randomization. Docetaxel at a dose of 75 mg/m<sup>2</sup> as an intravenous infusion every 21 days for 6 cycles, starting within 6 weeks after the start of the study drug, and in combination with prednisone/prednisolone at the discretion of the investigator.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 30 November 2016 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy         |
| Long term follow-up duration                              | 59 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | Belgium: 24   |
| Country: Number of subjects enrolled | Brazil: 53    |
| Country: Number of subjects enrolled | Bulgaria: 17  |
| Country: Number of subjects enrolled | Canada: 26    |
| Country: Number of subjects enrolled | China: 203    |
| Country: Number of subjects enrolled | Czechia: 13   |
| Country: Number of subjects enrolled | Finland: 24   |
| Country: Number of subjects enrolled | France: 43    |
| Country: Number of subjects enrolled | Germany: 54   |
| Country: Number of subjects enrolled | Israel: 28    |
| Country: Number of subjects enrolled | Italy: 17     |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Japan: 148             |
| Country: Number of subjects enrolled | Mexico: 14             |
| Country: Number of subjects enrolled | Netherlands: 33        |
| Country: Number of subjects enrolled | Poland: 17             |
| Country: Number of subjects enrolled | Russian Federation: 91 |
| Country: Number of subjects enrolled | Korea, Republic of: 85 |
| Country: Number of subjects enrolled | Spain: 75              |
| Country: Number of subjects enrolled | Sweden: 35             |
| Country: Number of subjects enrolled | Taiwan: 37             |
| Country: Number of subjects enrolled | United Kingdom: 29     |
| Country: Number of subjects enrolled | United States: 218     |
| Worldwide total number of subjects   | 1305                   |
| EEA total number of subjects         | 352                    |

Notes:

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### 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)                      | 477 |
| From 65 to 84 years                       | 821 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

This multinational study was conducted between 30-Nov-2016 First Subject First Visit and 11-Apr-2023 Last Subject Last Visit in 23 countries/regions: Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Finland, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Sweden, Taiwan, UK and US

### Pre-assignment

Screening details:

1306 subjects were randomly assigned in a 1:1 ratio to study treatment and 1305 subjects were considered valid for efficacy analyses. A total of 1302 subjects started treatment and were included to safety analyses.

### 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                | Investigator, Monitor, Data analyst, Carer, Subject, Assessor |

Blinding implementation details:

Double-blind

### Arms

|                              |                                       |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes                                   |
| <b>Arm title</b>             | Darolutamide (BAY1841788) + Docetaxel |

Arm description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started  $\leq 12$  weeks before randomization.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Darolutamide (Nubeqa, BAY1841788) |
| Investigational medicinal product code | BAY1841788                        |
| Other name                             |                                   |
| Pharmaceutical forms                   | Tablet                            |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.

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

Arm description:

Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started  $\leq 12$  weeks before randomization.

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

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**Dosage and administration details:**

The dosing of placebo is the same as for darolutamide

| <b>Number of subjects in period 1</b>                | Darolutamide<br>(BAY1841788) +<br>Docetaxel | Placebo + Docetaxel |
|--|---|---------------------|
|  |   |                     |
| Started  | 651   | 654                 |
| Started treatment                                    | 651   | 651                 |
| Completed  | 0   | 0                   |
| Not completed  | 651   | 654                 |
| Progressive disease – radiological<br>progression    | 90  | 133                 |
| Adverse event, serious fatal                         | 9   | 5                   |
| Physician decision                                   | 5   | 6                   |
| AE associated with clinical disease<br>progression   | 24  | 26                  |
| AE not associated w/ clinical disease<br>progression | 49  | 27                  |
| Progressive disease – clinical<br>progression        | 131   | 276                 |
| Consent withdrawn by subject                         | 26  | 40                  |
| Other  | 287   | 118                 |
| Study drug never administered                        | -   | 3                   |
| Non-compliance with study drug                       | 14  | 12                  |
| Lost to follow-up                                    | 4   | 2                   |
| Protocol deviation                                   | 1   | -                   |
| Additional primary malignancy                        | 11  | 6                   |

## Baseline characteristics

### Reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Darolutamide (BAY1841788) + Docetaxel |
| Reporting group description:  |                                       |
| Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started $\leq 12$ weeks before randomization. |                                       |
| Reporting group title   | Placebo + Docetaxel                   |
| Reporting group description:  |                                       |
| Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started $\leq 12$ weeks before randomization.   |                                       |

| Reporting group values   | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel | Total |
|--|---------------------------------------|---------------------|-------|
| Number of subjects   | 651                                   | 654                 | 1305  |
| Age Categorical  |                                       |                     |       |
| Units: Subjects  |                                       |                     |       |
| <=18 years   | 0                                     | 0                   | 0     |
| Between 18 and 65 years  | 243                                   | 234                 | 477   |
| >=65 years   | 408                                   | 420                 | 828   |
| Sex: Female, Male  |                                       |                     |       |
| Units: Subjects  |                                       |                     |       |
| Female   | 0                                     | 0                   | 0     |
| Male   | 651                                   | 654                 | 1305  |
| Ethnicity (NIH/OMB)  |                                       |                     |       |
| Units: Subjects  |                                       |                     |       |
| Hispanic or Latino   | 40                                    | 49                  | 89    |
| Not Hispanic or Latino   | 561                                   | 557                 | 1118  |
| Unknown or Not Reported  | 50                                    | 48                  | 98    |
| Race (NIH/OMB)   |                                       |                     |       |
| More than one race includes: "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", and "Multiple" |                                       |                     |       |
| Units: Subjects  |                                       |                     |       |
| American Indian or Alaska Native   | 0                                     | 0                   | 0     |
| Asian  | 231                                   | 245                 | 476   |
| Native Hawaiian or Other Pacific Islander  | 0                                     | 0                   | 0     |
| Black or African American  | 26                                    | 28                  | 54    |
| White  | 345                                   | 333                 | 678   |
| More than one race   | 6                                     | 2                   | 8     |
| Unknown or Not Reported  | 43                                    | 46                  | 89    |

## End points

### End points reporting groups

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Darolutamide (BAY1841788) + Docetaxel |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started  $\leq 12$  weeks before randomization.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Placebo + Docetaxel |
|-----------------------|---------------------|

Reporting group description:

Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started  $\leq 12$  weeks before randomization.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full analysis set (FAS) |
|----------------------------|-------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All subjects who were randomized were included in the FAS

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Safety analysis set (SAF) |
|----------------------------|---------------------------|

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

Subject analysis set description:

All randomized subjects who received at least 1 dose of darolutamide or placebo were included in the SAF.

Subjects were included in the darolutamide+docetaxel arm if they received any dose of darolutamide and were included in the placebo+docetaxel arm if they only received the placebo.

### Primary: OS from date of randomization until death from any cause - Number of events

|                 |   |
|-----------------|---|
| End point title | OS from date of randomization until death from any cause - Number of events |
|-----------------|---|

End point description:

Overall survival (OS) was defined as the time from the date of randomization until death from any cause.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

Long-term (Survival) follow-up period: After Active follow-up, patients continued to be contacted approximately every 12 weeks by phone. The end of the Survival follow-up period was defined as when the patient died, was lost to follow-up, withdrew consent, or at the end-of-study.

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

End point timeframe:

From randomization of the first subject until death from any cause up to 25 OCT 2021 cut-off date 533 OS events were reached (approximate 59 months)

|                               |                                       |                     |  |  |
|-------------------------------|---------------------------------------|---------------------|--|--|
| <b>End point values</b>       | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
| Subject group type            | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed   | 651 <sup>[1]</sup>                    | 654 <sup>[2]</sup>  |  |  |
| Units: Subjects               |                                       |                     |  |  |
| Number of subjects with event | 229                                   | 304                 |  |  |
| Number of subjects censored   | 422                                   | 350                 |  |  |

Notes:

[1] - FAS

[2] - FAS

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | OS - Inferential statistics                                 |
| Statistical analysis description:  |   |
| One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN). |   |
| Comparison groups  | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis  | 1305  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority <sup>[3]</sup>                                  |
| P-value  | < 0.0001 <sup>[4]</sup>                                     |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.675   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.568   |
| upper limit  | 0.801   |

Notes:

[3] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

[4] - One-sided p-value.

## Primary: OS from date of randomization until death from any cause - Month

|                 |   |
|-----------------|---|
| End point title | OS from date of randomization until death from any cause - Month <sup>[5]</sup> |
|-----------------|---|

End point description:

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

Long-term (Survival) follow-up period: After Active follow-up, patients continued to be contacted approximately every 12 weeks by phone. The end of the Survival follow-up period was defined as when the patient died, was lost to follow-up, withdrew consent, or at the end-of-study. Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.

99999 = Value cannot be estimated due to censored



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

End point timeframe:

From randomization of the first subject until death from any cause up to 25 OCT 2021 cut-off date 533 OS events were reached (approximate 59 months)

Notes:

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

Justification: Refer to inferential statistics table above under endpoint "Primary: OS from date of randomization until death from any cause - Number of events".

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel  |  |  |
|----------------------------------|---------------------------------------|----------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group      |  |  |
| Number of subjects analysed      | 651 <sup>[6]</sup>                    | 654 <sup>[7]</sup>   |  |  |
| Units: Month                     |                                       |                      |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                | 48.9 (44.4 to 99999) |  |  |

Notes:

[6] - FAS

[7] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with TEAEs

|                 |                               |
|-----------------|-------------------------------|
| End point title | Number of subjects with TEAEs |
|-----------------|-------------------------------|

End point description:

TEAEs = Treatment-emergent adverse events, were defined as any event(s) arising or worsening after the first dose of darolutamide or placebo, until 30 days after the last dose of darolutamide or placebo administration.

Number of Subjects Analyzed for arm "Darolutamide (BAY1841788) + Docetaxel" should be 652. One subject was randomized to the placebo+docetaxel arm but received at least one dose of darolutamide. This subject was included in the darolutamide+docetaxel arm in the analysis of all safety variables

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

End point timeframe:

From the first dose of darolutamide or placebo until 30 days after the last dose of darolutamide or placebo administration up to cut-off date for the final completion analysis 11 APR 2023 (approximately 77 months)

| End point values                             | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|--|---------------------------------------|---------------------|--|--|
| Subject group type                           | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed                  | 651 <sup>[8]</sup>                    | 650 <sup>[9]</sup>  |  |  |
| Units: Subjects                              |                                       |                     |  |  |
| Any TEAE                                     | 649                                   | 643                 |  |  |
| TESAE  | 306                                   | 276                 |  |  |
| TEAE leading to study drug dose modification | 172                                   | 112                 |  |  |
| TEAE leading to permanent stop of study drug | 90                                    | 69                  |  |  |

|   |     |     |  |  |
|---|-----|-----|--|--|
| TEAE leading to docetaxel dose modification     | 216 | 214 |  |  |
| TEAE leading to permanent stop of docetaxel     | 52  | 67  |  |  |
| Related to protocol-required procedure          | 69  | 64  |  |  |
| Any study drug-related TEAE                     | 344 | 309 |  |  |
| Study drug-related TESAE                        | 30  | 24  |  |  |
| Drug-related TEAE leading to dose modification  | 75  | 41  |  |  |
| Drug-related TEAE leading to stop of study drug | 25  | 13  |  |  |

Notes:

[8] - SAF: Number of Subjects Analyzed should be 652. Details refer to "End point description" above.

[9] - SAF

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to castration-resistant prostate cancer (CRPC) - Number of events

|                 |  |
|-----------------|--|
| End point title | Time to castration-resistant prostate cancer (CRPC) - Number of events |
|-----------------|--|

End point description:

Time to castration-resistant prostate cancer was defined as the time from randomization to the first occurrence of one of the following events: PSA progression, Radiological progression by bone lesions, or Radiological progression by soft tissue and visceral lesions.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the first occurrence of an CRPC event up to 25 OCT 2021 cut-off date approximately 59 months

| End point values              | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type            | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed   | 651 <sup>[10]</sup>                   | 654 <sup>[11]</sup> |  |  |
| Units: Subjects               |                                       |                     |  |  |
| Number of subjects with event | 225                                   | 391                 |  |  |
| Number of subjects censored   | 426                                   | 263                 |  |  |

Notes:

[10] - FAS

[11] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to castration-resistant prostate cancer (CRPC) - Month

|                 |   |
|-----------------|---|
| End point title | Time to castration-resistant prostate cancer (CRPC) - Month |
|-----------------|---|

End point description:

Time to castration-resistant prostate cancer was defined as the time from randomization to the first occurrence of one of the following events: PSA progression, Radiological progression by bone lesions, or Radiological progression by soft tissue and visceral lesions.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

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

End point timeframe:

From randomization of the first subject to the first occurrence of an CRPC event up to 25 OCT 2021 cut-off date approximately 59 months

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed      | 651 <sup>[12]</sup>                   | 654 <sup>[13]</sup> |  |  |
| Units: Months                    |                                       |                     |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                | 19.1 (16.5 to 21.8) |  |  |

Notes:

[12] - FAS

[13] - FAS

## Statistical analyses

|                            |                               |
|----------------------------|-------------------------------|
| Statistical analysis title | CRPC - Inferential statistics |
|----------------------------|-------------------------------|

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

|   |   |
|---|---|
| Comparison groups                       | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis | 1305  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority <sup>[14]</sup>                                 |
| P-value                                 | < 0.0001 <sup>[15]</sup>                                    |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.357   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.302   |
| upper limit                             | 0.421   |

Notes:

[14] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

[15] - One-sided p-value.

## Secondary: Time to pain progression - Number of events

|                 |   |
|-----------------|---|
| End point title | Time to pain progression - Number of events |
|-----------------|---|

End point description:

Time to pain progression was defined as the time from randomization to the first date a patient experienced pain progression.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the first occurrence of a pain progression event up to 25 OCT 2021 cut-off date approximately 59 months

| End point values              | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type            | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed   | 651 <sup>[16]</sup>                   | 654 <sup>[17]</sup> |  |  |
| Units: Subjects               |                                       |                     |  |  |
| Number of subjects with event | 222                                   | 248                 |  |  |
| Number of subjects censored   | 429                                   | 406                 |  |  |

Notes:

[16] - FAS

[17] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to pain progression - Month

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Time to pain progression - Month |
|-----------------|----------------------------------|

End point description:

Time to pain progression was defined as the time from randomization to the first date a patient experienced pain progression.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomization of the first subject to the first occurrence of a pain progression event up to 25 OCT 2021 cut-off date approximately 59 months |           |

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed      | 651 <sup>[18]</sup>                   | 654 <sup>[19]</sup> |  |  |
| Units: Months                    |                                       |                     |  |  |
| median (confidence interval 95%) | 99999 (30.5 to 99999)                 | 27.5 (22.0 to 36.1) |  |  |

Notes:

[18] - FAS

[19] - FAS

## Statistical analyses

| Statistical analysis title | Time to pain progression-Inferential statistics |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

|   |   |
|---|---|
| Comparison groups                       | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis | 1305  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority <sup>[20]</sup>                                 |
| P-value                                 | = 0.0058 <sup>[21]</sup>                                    |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.792   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.66  |
| upper limit                             | 0.95  |

Notes:

[20] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

[21] - One-sided p-value.

## Secondary: Symptomatic skeletal event free survival (SSE-FS) - Number of events

|                 |  |
|-----------------|--|
| End point title | Symptomatic skeletal event free survival (SSE-FS) - Number of events |
|-----------------|--|

End point description:

Symptomatic skeletal event-free survival (SSE-FS) was defined as the time from randomization to the first occurrence of an SSE or death from any cause, whichever occurred first.

Treatment period: treatment was provided for all patients, twice daily, until disease progression

(symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event or death from any cause, whichever occurred first up to 25 OCT 2021 cut-off date approximately 59 months

| End point values              | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type            | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed   | 651 <sup>[22]</sup>                   | 654 <sup>[23]</sup> |  |  |
| Units: Subjects               |                                       |                     |  |  |
| Number of subjects with event | 257                                   | 329                 |  |  |
| Number of subjects censored   | 394                                   | 325                 |  |  |

Notes:

[22] - FAS

[23] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Symptomatic skeletal event free survival (SSE-FS) - Month

|                 |   |
|-----------------|---|
| End point title | Symptomatic skeletal event free survival (SSE-FS) - Month |
|-----------------|---|

End point description:

Symptomatic skeletal event-free survival (SSE-FS) was defined as the time from randomization to the first occurrence of an SSE or death from any cause, whichever occurred first.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

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

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event or death from any cause, whichever occurred first up to 25 OCT 2021 cut-off date approximately 59 months

|                                  |                                       |                     |  |  |
|----------------------------------|---------------------------------------|---------------------|--|--|
| <b>End point values</b>          | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
| Subject group type               | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed      | 651 <sup>[24]</sup>                   | 654 <sup>[25]</sup> |  |  |
| Units: Months                    |                                       |                     |  |  |
| median (confidence interval 95%) | 51.2 (47.2 to 99999)                  | 39.7 (36.0 to 42.3) |  |  |

Notes:

[24] - FAS

[25] - FAS

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | SSE-FS - Inferential statistics                             |
| Statistical analysis description:  |   |
| One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN). |   |
| Comparison groups  | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis  | 1305  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority <sup>[26]</sup>                                 |
| P-value  | < 0.0001 <sup>[27]</sup>                                    |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.609   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.516   |
| upper limit  | 0.718   |

Notes:

[26] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

[27] - One-sided p-value.

## Secondary: Time to first symptomatic skeletal event (SSE) - Number of events

|                 |   |
|-----------------|---|
| End point title | Time to first symptomatic skeletal event (SSE) - Number of events |
|-----------------|---|

End point description:

Time to the first SSE was defined as the time from randomization to the first occurrence of an SSE. Identical to the definition used for SSE-FS. Death was not considered as an event in this endpoint.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event up to 25 OCT 2021 cut-

| End point values                  | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type                | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed       | 651 <sup>[28]</sup>                   | 654 <sup>[29]</sup> |  |  |
| Units: Subjects                   |                                       |                     |  |  |
| Number (%) of subjects with event | 95                                    | 108                 |  |  |
| Number (%) of subjects censored   | 556                                   | 546                 |  |  |

Notes:

[28] - FAS

[29] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first symptomatic skeletal event (SSE) - Month

|                 |  |
|-----------------|--|
| End point title | Time to first symptomatic skeletal event (SSE) - Month |
|-----------------|--|

End point description:

Time to the first SSE was defined as the time from randomization to the first occurrence of an SSE. Identical to the definition used for SSE-FS. Death was not considered as an event in this endpoint.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

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

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event up to 25 OCT 2021 cut-off date approximately 59 months

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel    |  |  |
|----------------------------------|---------------------------------------|------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group        |  |  |
| Number of subjects analysed      | 651 <sup>[30]</sup>                   | 654 <sup>[31]</sup>    |  |  |
| Units: Months                    |                                       |                        |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                | 99999 (99999 to 99999) |  |  |

Notes:

[30] - FAS

[31] - FAS

### Statistical analyses



|   |   |
|---|---|
| <b>Statistical analysis title</b>   | SSE - Inferential statistics                                |
| Statistical analysis description:   |   |
| One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN). |   |
| Comparison groups   | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis   | 1305  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority <sup>[32]</sup>                                 |
| P-value   | = 0.0081 <sup>[33]</sup>                                    |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.712   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.539   |
| upper limit   | 0.94  |

Notes:

[32] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

[33] - One-sided p-value.

## Secondary: Time to initiation of subsequent antineoplastic therapy - Number of events

|                 |  |
|-----------------|--|
| End point title | Time to initiation of subsequent antineoplastic therapy - Number of events |
|-----------------|--|

End point description:

Time to initiation of subsequent systemic antineoplastic therapy was defined as the time from randomization to the initiation of first subsequent systemic antineoplastic therapy.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the initiation of first subsequent systemic antineoplastic therapy up to 25 OCT 2021 cut-off date approximately 59 months

| End point values                  | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type                | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed       | 651 <sup>[34]</sup>                   | 654 <sup>[35]</sup> |  |  |
| Units: Subjects                   |                                       |                     |  |  |
| Number (%) of subjects with event | 219                                   | 395                 |  |  |
| Number (%) of subjects censored   | 432                                   | 259                 |  |  |

Notes:

[34] - FAS

[35] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to initiation of subsequent antineoplastic therapy - Month

|                 |   |
|-----------------|---|
| End point title | Time to initiation of subsequent antineoplastic therapy - Month |
|-----------------|---|

End point description:

Time to initiation of subsequent systemic antineoplastic therapy was defined as the time from randomization to the initiation of first subsequent systemic antineoplastic therapy.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

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

End point timeframe:

From randomization of the first subject to the initiation of first subsequent systemic antineoplastic therapy up to 25 OCT 2021 cut-off date approximately 59 months

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed      | 651 <sup>[36]</sup>                   | 654 <sup>[37]</sup> |  |  |
| Units: Months                    |                                       |                     |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                | 25.3 (23.1 to 28.8) |  |  |

Notes:

[36] - FAS

[37] - FAS

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Inferential statistics |
|----------------------------|------------------------|

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

|                   |   |
|-------------------|---|
| Comparison groups | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
|-------------------|---|

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 1305                        |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[38]</sup> |
| P-value                                 | < 0.0001 <sup>[39]</sup>    |
| Method                                  | Logrank                     |
| Parameter estimate                      | Log hazard ratio            |
| Point estimate                          | 0.388                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.328                       |
| upper limit                             | 0.458                       |

Notes:

[38] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

[39] - One-sided p-value.

## Secondary: Time to worsening of disease-related physical symptoms - Number of events

|                 |   |
|-----------------|---|
| End point title | Time to worsening of disease-related physical symptoms - Number of events |
|-----------------|---|

End point description:

Time to worsening of disease-related physical symptoms was defined as the time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the first increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire up to 25 OCT 2021 cut-off date approximately 59 months

| End point values                  | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type                | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed       | 651 <sup>[40]</sup>                   | 654 <sup>[41]</sup> |  |  |
| Units: Subjects                   |                                       |                     |  |  |
| Number (%) of subjects with event | 351                                   | 308                 |  |  |
| Number (%) of subjects censored   | 300                                   | 346                 |  |  |

Notes:

[40] - FAS

[41] - FAS

## Statistical analyses

**Secondary: Time to worsening of disease-related physical symptoms - Month**

|                 |  |
|-----------------|--|
| End point title | Time to worsening of disease-related physical symptoms - Month |
|-----------------|--|

## End point description:

Time to worsening of disease-related physical symptoms was defined as the time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

## End point timeframe:

From randomization of the first subject to the first increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire up to 25 OCT 2021 cut-off date approximately 59 months

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|----------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed      | 651 <sup>[42]</sup>                   | 654 <sup>[43]</sup> |  |  |
| Units: Months                    |                                       |                     |  |  |
| median (confidence interval 95%) | 19.3 (13.8 to 24.8)                   | 19.4 (15.4 to 27.6) |  |  |

## Notes:

[42] - FAS

[43] - FAS

**Statistical analyses**

|                            |   |
|----------------------------|---|
| Statistical analysis title | Worsening of disease - Inferential statistics |
|----------------------------|---|

## Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. ≥ULN).

|   |   |
|---|---|
| Comparison groups                       | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis | 1305  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority <sup>[44]</sup>                                 |
| P-value                                 | = 0.7073 <sup>[45]</sup>                                    |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 1.043   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.894   |
| upper limit         | 1.217   |

Notes:

[44] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

[45] - One-sided p-value.

## Secondary: Time to initiation of opioid use for ≥7 consecutive days - Number of events

|                 |   |
|-----------------|---|
| End point title | Time to initiation of opioid use for ≥7 consecutive days - Number of events |
|-----------------|---|

End point description:

Time to the initiation of opioid use for ≥7 consecutive days was defined as the time from randomization to the date of the first opioid use for ≥7 consecutive days. Data of opioid use related to cancer pain was included in the analysis, and opioid use for non-malignant causes was excluded.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

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

End point timeframe:

From randomization of the first subject to the first opioid use for ≥7 consecutive days up to 25 OCT 2021 cut-off date approximately 59 months

| End point values              | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel |  |  |
|-------------------------------|---------------------------------------|---------------------|--|--|
| Subject group type            | Reporting group                       | Reporting group     |  |  |
| Number of subjects analysed   | 651 <sup>[46]</sup>                   | 654 <sup>[47]</sup> |  |  |
| Units: Subjects               |                                       |                     |  |  |
| Number of subjects with event | 92                                    | 117                 |  |  |
| Number of subjects censored   | 559                                   | 537                 |  |  |

Notes:

[46] - FAS

[47] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to initiation of opioid use for ≥7 consecutive days - Month

|                 |  |
|-----------------|--|
| End point title | Time to initiation of opioid use for ≥7 consecutive days - Month |
|-----------------|--|

End point description:

Time to the initiation of opioid use for ≥7 consecutive days was defined as the time from randomization to the date of the first opioid use for ≥7 consecutive days. Data of opioid use related to cancer pain was

included in the analysis, and opioid use for non-malignant causes was excluded.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomization of the first subject to the first opioid use for $\geq 7$ consecutive days up to 25 OCT 2021 cut-off date approximately 59 months |           |

| End point values                 | Darolutamide (BAY1841788) + Docetaxel | Placebo + Docetaxel    |  |  |
|----------------------------------|---------------------------------------|------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group        |  |  |
| Number of subjects analysed      | 651 <sup>[48]</sup>                   | 654 <sup>[49]</sup>    |  |  |
| Units: Months                    |                                       |                        |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                | 99999 (99999 to 99999) |  |  |

Notes:

[48] - FAS

[49] - FAS

## Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Initiation of opioid - Inferential statistics               |
| Statistical analysis description:  |   |
| One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. $\geq$ ULN). |   |
| Comparison groups  | Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel |
| Number of subjects included in analysis  | 1305  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority <sup>[50]</sup>                                 |
| P-value  | = 0.0037 <sup>[51]</sup>                                    |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.688   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.523   |
| upper limit  | 0.906   |

Notes:

[50] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs.  $\geq$ ULN).

[51] - One-sided p-value.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 30 days after the last administration, including adverse event of deaths (all causes) at any time during the study, up to cut-off date for the final completion analysis 11 APR 2023 (approximately 77 months).

Adverse event reporting additional description:

TEAEs were defined as any event arising or worsening after the first dose of darolutamide or placebo, until 30 days after the last dose of darolutamide or placebo administration.

Events causally related to treatment were considered as events causally related to either darolutamide/Docetaxel or Placebo/Docetaxel.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Placebo + Docetaxel |
|-----------------------|---------------------|

Reporting group description:

Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started  $\leq 12$  weeks before randomization.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Darolutamide (BAY1841788) + Docetaxel |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started  $\leq 12$  weeks before randomization.

| Serious adverse events  | Placebo + Docetaxel | Darolutamide (BAY1841788) + Docetaxel |  |
|---|---------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events                   |                     |                                       |  |
| subjects affected / exposed   | 276 / 650 (42.46%)  | 306 / 652 (46.93%)                    |  |
| number of deaths (all causes)                                       | 305                 | 231                                   |  |
| number of deaths resulting from adverse events                      | 26                  | 29                                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                                       |  |
| Medulloblastoma   |                     |                                       |  |
| subjects affected / exposed   | 1 / 650 (0.15%)     | 0 / 652 (0.00%)                       |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 0                                 |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0                                 |  |
| Brain neoplasm malignant  |                     |                                       |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon cancer                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Laryngeal cancer                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma in situ                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to lung                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sebaceous carcinoma                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myelofibrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal adenocarcinoma                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal carcinoma                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pancreatic carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Papillary thyroid cancer                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Phaeochromocytoma                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal adenocarcinoma                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of lung                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transitional cell carcinoma                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Tumour pain                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 4 / 652 (0.61%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Waldenstrom's macroglobulinaemia                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cancer pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm malignant                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to central nervous system            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Thyroid cancer                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour compression                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oral papilloma                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic malignant melanoma                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatocellular carcinoma                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestine adenocarcinoma                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic aneurysm                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Aortic dissection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hypertensive crisis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphoedema                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Phlebitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (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                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive emergency                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial occlusive disease                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Spinal laminectomy                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardioversion                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip arthroplasty                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia repair                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orchidectomy                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bilateral orchidectomy                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radical prostatectomy                           |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Cancer surgery                                       |                 |                 |  |
| subjects affected / exposed                          | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Atrial appendage closure                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Spinal fusion surgery                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 2 / 650 (0.31%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Fatigue  |                 |                 |  |
| subjects affected / exposed                          | 2 / 650 (0.31%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hernia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                                    |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 650 (0.31%)  | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pain  |                  |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyrexia   |                  |                 |  |
| subjects affected / exposed                     | 15 / 650 (2.31%) | 9 / 652 (1.38%) |  |
| occurrences causally related to treatment / all | 10 / 15          | 3 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sudden death                                    |                  |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%)  | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 2           |  |
| General physical health deterioration           |                  |                 |  |
| subjects affected / exposed                     | 4 / 650 (0.62%)  | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 4            | 0 / 1           |  |
| Cardiac death                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Unevaluable event                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Non-cardiac chest pain                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Death   |                  |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                       | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all   | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 2           | 0 / 1           |  |
| Immune system disorders                           |                 |                 |  |
| Anaphylactic reaction                             |                 |                 |  |
| subjects affected / exposed                       | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all   | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Hypersensitivity                                  |                 |                 |  |
| subjects affected / exposed                       | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Social circumstances                              |                 |                 |  |
| Loss of personal independence in daily activities |                 |                 |  |
| subjects affected / exposed                       | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| 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          |                 |                 |  |
| Benign prostatic hyperplasia                      |                 |                 |  |
| subjects affected / exposed                       | 1 / 650 (0.15%) | 0 / 652 (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                       | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Prostatomegaly                                    |                 |                 |  |
| subjects affected / exposed                       | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Prostatic obstruction                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchiectasis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis chronic                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Interstitial lung disease                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 650 (0.77%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 4 / 6           | 1 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Nasal polyps                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 4 / 652 (0.61%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax spontaneous                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 4 / 650 (0.62%) | 6 / 652 (0.92%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 2 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Respiratory failure                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Obstructive airways disorder                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Insomnia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device deposit issue                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device dislocation                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device occlusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product contamination                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertransaminaemia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Drug-induced liver injury                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biliary obstruction                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 8 / 650 (1.23%) | 6 / 652 (0.92%) |  |
| occurrences causally related to treatment / all | 6 / 10          | 4 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 4 / 650 (0.62%) | 5 / 652 (0.77%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 4 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biopsy lymph gland                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood glucose increased                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphocyte count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                      |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 10 / 650 (1.54%) | 18 / 652 (2.76%) |  |
| occurrences causally related to treatment / all | 10 / 10          | 24 / 24          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Platelet count decreased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| White blood cell count decreased                |                  |                  |  |
| subjects affected / exposed                     | 4 / 650 (0.62%)  | 2 / 652 (0.31%)  |  |
| occurrences causally related to treatment / all | 4 / 4            | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| White blood cell count increased                |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatic specific antigen abnormal             |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (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  |                  |                  |  |
| Tendon rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaesthetic complication cardiac                |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ankle fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 650 (0.31%)  | 2 / 652 (0.31%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extradural haematoma                            |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibula fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Snake bite                                      |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic fracture                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post laminectomy syndrome                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin laceration                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Limb injury                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament rupture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Hydrocele                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 4 / 652 (0.61%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block complete                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 1           |  |
| Cardiac failure                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiomyopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 4 / 652 (0.61%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular extrasystoles                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (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 / 650 (0.15%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (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                        |                 |                 |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Aphasia   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery thrombosis                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebellar syndrome                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 5 / 652 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Depressed level of consciousness                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage intracranial                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (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                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoaesthesia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| IIIrd nerve paralysis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral sensory neuropathy                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord compression                         |                 |                 |  |
| subjects affected / exposed                     | 7 / 650 (1.08%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 5 / 650 (0.77%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery occlusion                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lacunar infarction                              |                 |                 |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vagus nerve disorder                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinson's disease                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Basal ganglia infarction                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (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 / 650 (0.15%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Anaemia   |                  |                  |  |
| subjects affected / exposed                     | 4 / 650 (0.62%)  | 5 / 652 (0.77%)  |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 39 / 650 (6.00%) | 40 / 652 (6.13%) |  |
| occurrences causally related to treatment / all | 38 / 44          | 39 / 40          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Granulocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 14 / 650 (2.15%) | 12 / 652 (1.84%) |  |
| occurrences causally related to treatment / all | 16 / 17          | 17 / 17          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelosuppression                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukopenia                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 650 (0.31%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bicytopenia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone marrow oedema syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune thrombocytopenia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vestibular disorder                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 5 / 652 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic retinopathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Macular oedema                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal detachment                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epiretinal membrane                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastric ulcer                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal discomfort                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal fistula                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dental caries                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 4 / 652 (0.61%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer perforation                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hiatus hernia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal haemorrhage                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal toxicity                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal strangulation                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal polyp                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Drug eruption                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin mass                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 6 / 650 (0.92%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus bladder                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urethral                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis haemorrhagic                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysuria   |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 650 (0.62%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Micturition disorder                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary bladder haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Urinary incontinence                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage urinary tract                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (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                     | 3 / 650 (0.46%) | 5 / 652 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract pain                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder tamponade                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary fistula                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 6 / 650 (0.92%) | 5 / 652 (0.77%) |  |
| occurrences causally related to treatment / all | 2 / 6           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Ureterolithiasis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 4 / 652 (0.61%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant urinary tract obstruction             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postrenal failure                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 6 / 650 (0.92%) | 6 / 652 (0.92%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 6 / 650 (0.92%) | 6 / 652 (0.92%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Groin pain                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle spasms                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoporosis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 5 / 652 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periarthritis                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rheumatoid arthritis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal osteoarthritis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Trigger finger                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pubic pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis of jaw                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal stenosis                                 |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neck pain                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Appendicitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacteraemia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 21 / 650 (3.23%) | 16 / 652 (2.45%) |  |
| occurrences causally related to treatment / all | 5 / 22           | 8 / 17           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Cellulitis                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 650 (0.31%)  | 0 / 652 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile colitis                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 650 (0.00%)  | 1 / 652 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystitis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 650 (0.15%)  | 0 / 652 (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                     | 2 / 650 (0.31%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epididymitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epstein-Barr virus infection                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (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                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fournier's gangrene                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis clostridial                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gingivitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Laryngitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myelitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nasopharyngitis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyomyositis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 6 / 650 (0.92%) | 6 / 652 (0.92%) |  |
| occurrences causally related to treatment / all | 2 / 6           | 3 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sialoadenitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tonsillitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 5 / 650 (0.77%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 7 / 650 (1.08%) | 7 / 652 (1.07%) |  |
| occurrences causally related to treatment / all | 0 / 11          | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic sepsis                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                   | 0 / 650 (0.00%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Spinal cord infection   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pulmonary sepsis  |                 |                 |  |
| subjects affected / exposed                                   | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all               | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 2           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| West Nile viral infection                                     |                 |                 |  |
| subjects affected / exposed                                   | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Enterocolitis infectious                                      |                 |                 |  |
| subjects affected / exposed                                   | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pyelonephritis  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 650 (0.15%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial   |                 |                 |  |
| subjects affected / exposed                                   | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all               | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Anorectal infection   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular device infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| COVID-19  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 2 / 652 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| COVID-19 pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 7 / 652 (1.07%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 4           |  |
| Arthritis infective                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Cachexia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gout  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 3 / 652 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 650 (0.15%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour lysis syndrome                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Vitamin B12 deficiency                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 650 (0.46%) | 0 / 652 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperferritinaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 650 (0.00%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 650 (0.31%) | 1 / 652 (0.15%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| 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>                     | Placebo + Docetaxel | Darolutamide (BAY1841788) + Docetaxel |  |
|---|---------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events |                     |                                       |  |
| subjects affected / exposed                           | 634 / 650 (97.54%)  | 636 / 652 (97.55%)                    |  |
| Vascular disorders                                    |                     |                                       |  |
| Hot flush   |                     |                                       |  |
| subjects affected / exposed                           | 122 / 650 (18.77%)  | 128 / 652 (19.63%)                    |  |
| occurrences (all)                                     | 136                 | 141                                   |  |

|  |  |   |  |
|--|--|---|--|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 61 / 650 (9.38%)<br>72   | 86 / 652 (13.19%)<br>112  |  |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Malaise<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 83 / 650 (12.77%)<br>110<br><br>42 / 650 (6.46%)<br>48<br><br>169 / 650 (26.00%)<br>194<br><br>67 / 650 (10.31%)<br>97<br><br>215 / 650 (33.08%)<br>287<br><br>65 / 650 (10.00%)<br>83 | 84 / 652 (12.88%)<br>104<br><br>30 / 652 (4.60%)<br>36<br><br>175 / 652 (26.84%)<br>206<br><br>58 / 652 (8.90%)<br>78<br><br>222 / 652 (34.05%)<br>291<br><br>71 / 652 (10.89%)<br>89 |  |
| Respiratory, thoracic and mediastinal disorders<br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 34 / 650 (5.23%)<br>38<br><br>71 / 650 (10.92%)<br>78<br><br>73 / 650 (11.23%)<br>83   | 38 / 652 (5.83%)<br>50<br><br>62 / 652 (9.51%)<br>73<br><br>87 / 652 (13.34%)<br>103  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 80 / 650 (12.31%)<br>93  | 77 / 652 (11.81%)<br>85   |  |

|  |                    |                    |  |
|--|--------------------|--------------------|--|
| Investigations                                 |                    |                    |  |
| Blood alkaline phosphatase increased           |                    |                    |  |
| subjects affected / exposed                    | 43 / 650 (6.62%)   | 45 / 652 (6.90%)   |  |
| occurrences (all)                              | 53                 | 53                 |  |
| White blood cell count decreased               |                    |                    |  |
| subjects affected / exposed                    | 142 / 650 (21.85%) | 155 / 652 (23.77%) |  |
| occurrences (all)                              | 360                | 395                |  |
| Weight increased                               |                    |                    |  |
| subjects affected / exposed                    | 105 / 650 (16.15%) | 116 / 652 (17.79%) |  |
| occurrences (all)                              | 130                | 147                |  |
| Weight decreased                               |                    |                    |  |
| subjects affected / exposed                    | 37 / 650 (5.69%)   | 27 / 652 (4.14%)   |  |
| occurrences (all)                              | 37                 | 32                 |  |
| Neutrophil count decreased                     |                    |                    |  |
| subjects affected / exposed                    | 151 / 650 (23.23%) | 165 / 652 (25.31%) |  |
| occurrences (all)                              | 415                | 432                |  |
| Aspartate aminotransferase increased           |                    |                    |  |
| subjects affected / exposed                    | 66 / 650 (10.15%)  | 87 / 652 (13.34%)  |  |
| occurrences (all)                              | 84                 | 120                |  |
| Alanine aminotransferase increased             |                    |                    |  |
| subjects affected / exposed                    | 81 / 650 (12.46%)  | 99 / 652 (15.18%)  |  |
| occurrences (all)                              | 103                | 132                |  |
| Injury, poisoning and procedural complications |                    |                    |  |
| Fall   |                    |                    |  |
| subjects affected / exposed                    | 33 / 650 (5.08%)   | 45 / 652 (6.90%)   |  |
| occurrences (all)                              | 37                 | 64                 |  |
| Nervous system disorders                       |                    |                    |  |
| Peripheral sensory neuropathy                  |                    |                    |  |
| subjects affected / exposed                    | 68 / 650 (10.46%)  | 65 / 652 (9.97%)   |  |
| occurrences (all)                              | 72                 | 74                 |  |
| Paraesthesia                                   |                    |                    |  |
| subjects affected / exposed                    | 55 / 650 (8.46%)   | 42 / 652 (6.44%)   |  |
| occurrences (all)                              | 66                 | 45                 |  |
| Neuropathy peripheral                          |                    |                    |  |
| subjects affected / exposed                    | 68 / 650 (10.46%)  | 77 / 652 (11.81%)  |  |
| occurrences (all)                              | 72                 | 91                 |  |



|   |                           |                           |  |
|---|---------------------------|---------------------------|--|
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                                   | 29 / 650 (4.46%)<br>40    | 38 / 652 (5.83%)<br>44    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 49 / 650 (7.54%)<br>58    | 59 / 652 (9.05%)<br>72    |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                       | 80 / 650 (12.31%)<br>84   | 71 / 652 (10.89%)<br>88   |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                       | 52 / 650 (8.00%)<br>64    | 60 / 652 (9.20%)<br>69    |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 164 / 650 (25.23%)<br>227 | 185 / 652 (28.37%)<br>276 |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                     | 67 / 650 (10.31%)<br>103  | 62 / 652 (9.51%)<br>108   |  |
| Eye disorders<br>Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)          | 43 / 650 (6.62%)<br>47    | 38 / 652 (5.83%)<br>40    |  |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)          | 58 / 650 (8.92%)<br>69    | 53 / 652 (8.13%)<br>63    |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                      | 57 / 650 (8.77%)<br>69    | 67 / 652 (10.28%)<br>87   |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 134 / 650 (20.62%)<br>174 | 117 / 652 (17.94%)<br>150 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                       | 157 / 650 (24.15%)<br>225 | 168 / 652 (25.77%)<br>229 |  |
| Constipation  |                           |                           |  |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| subjects affected / exposed                     | 132 / 650 (20.31%) | 149 / 652 (22.85%) |  |
| occurrences (all)                               | 162                | 202                |  |
| Abdominal pain                                  |                    |                    |  |
| subjects affected / exposed                     | 37 / 650 (5.69%)   | 36 / 652 (5.52%)   |  |
| occurrences (all)                               | 40                 | 40                 |  |
| Skin and subcutaneous tissue disorders          |                    |                    |  |
| Rash  |                    |                    |  |
| subjects affected / exposed                     | 45 / 650 (6.92%)   | 53 / 652 (8.13%)   |  |
| occurrences (all)                               | 58                 | 64                 |  |
| Nail discolouration                             |                    |                    |  |
| subjects affected / exposed                     | 52 / 650 (8.00%)   | 50 / 652 (7.67%)   |  |
| occurrences (all)                               | 52                 | 51                 |  |
| Dry skin  |                    |                    |  |
| subjects affected / exposed                     | 35 / 650 (5.38%)   | 48 / 652 (7.36%)   |  |
| occurrences (all)                               | 37                 | 54                 |  |
| Alopecia  |                    |                    |  |
| subjects affected / exposed                     | 264 / 650 (40.62%) | 267 / 652 (40.95%) |  |
| occurrences (all)                               | 265                | 268                |  |
| Pruritus  |                    |                    |  |
| subjects affected / exposed                     | 52 / 650 (8.00%)   | 46 / 652 (7.06%)   |  |
| occurrences (all)                               | 62                 | 54                 |  |
| Renal and urinary disorders                     |                    |                    |  |
| Pollakiuria                                     |                    |                    |  |
| subjects affected / exposed                     | 43 / 650 (6.62%)   | 31 / 652 (4.75%)   |  |
| occurrences (all)                               | 47                 | 33                 |  |
| Haematuria                                      |                    |                    |  |
| subjects affected / exposed                     | 36 / 650 (5.54%)   | 59 / 652 (9.05%)   |  |
| occurrences (all)                               | 43                 | 73                 |  |
| Musculoskeletal and connective tissue disorders |                    |                    |  |
| Pain in extremity                               |                    |                    |  |
| subjects affected / exposed                     | 78 / 650 (12.00%)  | 104 / 652 (15.95%) |  |
| occurrences (all)                               | 95                 | 148                |  |
| Myalgia   |                    |                    |  |
| subjects affected / exposed                     | 65 / 650 (10.00%)  | 74 / 652 (11.35%)  |  |
| occurrences (all)                               | 84                 | 103                |  |
| Muscular weakness                               |                    |                    |  |

|                                    |                    |                    |  |
|------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed        | 48 / 650 (7.38%)   | 51 / 652 (7.82%)   |  |
| occurrences (all)                  | 54                 | 59                 |  |
| Bone pain                          |                    |                    |  |
| subjects affected / exposed        | 82 / 650 (12.62%)  | 80 / 652 (12.27%)  |  |
| occurrences (all)                  | 96                 | 91                 |  |
| Back pain                          |                    |                    |  |
| subjects affected / exposed        | 121 / 650 (18.62%) | 128 / 652 (19.63%) |  |
| occurrences (all)                  | 147                | 154                |  |
| Arthralgia                         |                    |                    |  |
| subjects affected / exposed        | 173 / 650 (26.62%) | 186 / 652 (28.53%) |  |
| occurrences (all)                  | 249                | 270                |  |
| Infections and infestations        |                    |                    |  |
| Urinary tract infection            |                    |                    |  |
| subjects affected / exposed        | 63 / 650 (9.69%)   | 57 / 652 (8.74%)   |  |
| occurrences (all)                  | 92                 | 91                 |  |
| Upper respiratory tract infection  |                    |                    |  |
| subjects affected / exposed        | 46 / 650 (7.08%)   | 57 / 652 (8.74%)   |  |
| occurrences (all)                  | 52                 | 73                 |  |
| Nasopharyngitis                    |                    |                    |  |
| subjects affected / exposed        | 46 / 650 (7.08%)   | 46 / 652 (7.06%)   |  |
| occurrences (all)                  | 56                 | 69                 |  |
| Metabolism and nutrition disorders |                    |                    |  |
| Decreased appetite                 |                    |                    |  |
| subjects affected / exposed        | 86 / 650 (13.23%)  | 121 / 652 (18.56%) |  |
| occurrences (all)                  | 96                 | 157                |  |
| Hyperglycaemia                     |                    |                    |  |
| subjects affected / exposed        | 61 / 650 (9.38%)   | 77 / 652 (11.81%)  |  |
| occurrences (all)                  | 74                 | 100                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 20 September 2016 | Protocol Amendment 1, dated 20 SEP 2016, was valid only for centers located in China. The main modification was: <ul style="list-style-type: none"><li>• Addition of new China specific pharmacokinetic (PK) sub-study</li></ul>  |
| 04 October 2016   | Protocol Amendment 2, dated 04 OCT 2016, was globally implemented. The main modifications were: <ul style="list-style-type: none"><li>• New drug-drug interaction data added</li><li>• Clarification of PK analysis<ul style="list-style-type: none"><li>o Patients participating to the detailed PK analysis (dense PK sampling) had received at least one cycle of docetaxel</li><li>o Clarified the timing of the sparse PK sampling</li><li>o Additional analysis of docetaxel in all the randomized patients</li></ul></li><li>• Addition of non-protein-bound (free) testosterone analysis</li></ul>  |
| 04 November 2016  | Protocol Amendment 3, dated 04 NOV 2016, was valid only for centers located in UK. The main modification was: <ul style="list-style-type: none"><li>• List of acceptable effective contraception methods to be used was added by request of the Medicines and Healthcare Products Regulatory Agency (MHRA)</li></ul>  |
| 31 January 2017   | Protocol Amendment 4, dated 31 JAN 2017, was valid only for centers located in Japan. The main modification was: <ul style="list-style-type: none"><li>• Added reporting requirements for medical device failures for imported and non-approved third-party devices used in Bayer-sponsored clinical trials in Japan to the PMDA, IECs/IRBs and investigators</li></ul>   |
| 12 February 2018  | Protocol Amendment 5, dated 12 FEB 2018, was globally implemented. The main modifications were: <ul style="list-style-type: none"><li>• New drug-drug interaction data added</li><li>• Modification of the dosing language to align darolutamide dosing wording across the development program</li><li>• Clarification of docetaxel dosage and administration in accordance with the label and clarified that the first cycle of docetaxel should be administered within 6 weeks after start of study drug instead of 6 weeks after randomization</li><li>• Guidance on laboratory tests before each docetaxel cycle to be in line with docetaxel label requirements</li><li>• Clarification added for the evaluation of soft tissue and visceral lesions; these were to be performed using the same radiological methods and assessed by RECIST criteria</li><li>• ADT switch to LHRH agonist was added to the list of prohibited concomitant medications and treatments and a clarification was added to allow an ADT switch to an antagonist during study treatment</li><li>• Collection of whole blood sample for pharmacogenetics test allowed at other visits if missed at Visit 1</li><li>• Clarification added for:<ul style="list-style-type: none"><li>o Unblinding in non-emergency situations was not permitted</li><li>o For PK sampling</li><li>o For laboratory safety assessments</li></ul></li></ul> |

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| 10 December 2019 | <p>Protocol Amendment 6, dated 10 DEC 2019, was globally implemented. The main modifications were:</p> <ul style="list-style-type: none"> <li>• Option to continue darolutamide treatment in a separate program was added for those patients who are ongoing on darolutamide treatment; patients assigned to placebo would discontinue treatment and complete the study</li> <li>• Additional survival sweeps were added</li> <li>• Detailed information on darolutamide drug-drug interactions was removed and information on the effect of darolutamide on the PK of docetaxel was updated</li> <li>• Guidance and cautions for specific drug-drug interactions were removed based on new data on these interactions becoming available</li> <li>• AE reporting was modified to clarify that disease progression should not be reported as an AE; only the associated signs and symptoms should be reported as AEs</li> <li>• In a subset of patients, additional determination of total and free testosterone was added to be performed also at the EOT Visit</li> </ul> |
| 26 May 2020      | <p>Protocol Amendment 7, dated 26 MAY 2020, was globally implemented. The main modifications were:</p> <ul style="list-style-type: none"> <li>• Planned second interim analysis was removed due to the implications of the COVID-19 pandemic on the conduct of study procedures and data collection at the study sites. The risk for not achieving the needed quality of data for a formal analysis at that point in time was considered to be too high</li> <li>• Clarification added for biomarker analysis and reporting</li> <li>• Added text regarding ranking of secondary endpoints</li> <li>• Due to removal of interim analysis 2, the sentence regarding alpha-spending was removed and a statement about beta-spending was added for clarification</li> </ul>  |
| 30 August 2021   | <p>Protocol Amendment 8, dated 30 AUG 2021 was valid only for centers located in Japan. The main modifications were:</p> <ul style="list-style-type: none"> <li>• To minimize the burden for subjects still enrolled after the study reached primary completion, the number of procedures will be reduced to a minimum, to guarantee patient treatment continuation and safety</li> <li>• Japanese subjects will be provided the opportunity to continue treatment at the discretion of the investigator</li> </ul>   |
| 02 August 2022   | <p>Protocol Amendment 9, dated 02 AUG 2022 was valid only for centers located in Japan. However, it was prepared as a consolidated protocol and therefore also includes the latest global protocol version 5.0 (amendment 7). It provided guidance on the criteria for study drug discontinuation in the event of a suspected drug-induced liver injury (DILI) because of newly identified safety data across darolutamide clinical trials, including cases of idiosyncratic hepatic reactions that were reversible upon treatment discontinuation.</p>   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported