



## Clinical trial results:

### A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects with Metastatic Hormonesensitive Prostate Cancer (mHSPC)

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2015-000735-32             |
| Trial protocol           | SE GB HU DE ES CZ PL RO IT |
| Global end of trial date |                            |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 29 March 2022 |
| First version publication date | 29 March 2022 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | 56021927PCR3002 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02489318 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Aragon Pharmaceuticals, Inc  |
| Sponsor organisation address | 10990 Wilshire Blvd., Suite 440, Los Angeles, CA, United States, 90024             |
| Public contact               | Clinical Registry Group, Aragon Pharmaceuticals, Inc, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Aragon Pharmaceuticals, Inc, ClinicalTrialsEU@its.jnj.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                                       | Interim           |
| Date of interim/final analysis                       | 07 September 2020 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 07 September 2020 |
| Global end of trial reached?                         | No                |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to determine if the addition of apalutamide to androgen deprivation therapy (ADT) provides superior efficacy in improving overall survival (OS) or radiographic progression-free survival (rPFS) for subjects with castration-sensitive prostate cancer mCSPC.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. The safety evaluations included monitoring of adverse events, clinical laboratory parameters (hematology, serum chemistry, fasting lipids, Thyroid stimulating hormone [TSH] and Prostate-specific antigen [PSA]), vital sign measurements, physical examinations, electrocardiograms, (collected at screening only) and Eastern Cooperative Oncology Group performance score.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 09 December 2015 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 37           |
| Country: Number of subjects enrolled | Australia: 11           |
| Country: Number of subjects enrolled | Brazil: 92              |
| Country: Number of subjects enrolled | Canada: 30              |
| Country: Number of subjects enrolled | China: 94               |
| Country: Number of subjects enrolled | Czechia: 31             |
| Country: Number of subjects enrolled | Germany: 17             |
| Country: Number of subjects enrolled | Spain: 20               |
| Country: Number of subjects enrolled | France: 16              |
| Country: Number of subjects enrolled | United Kingdom: 36      |
| Country: Number of subjects enrolled | Hungary: 24             |
| Country: Number of subjects enrolled | Israel: 14              |
| Country: Number of subjects enrolled | Italy: 34               |
| Country: Number of subjects enrolled | Japan: 51               |
| Country: Number of subjects enrolled | Korea, Republic of: 76  |
| Country: Number of subjects enrolled | Mexico: 48              |
| Country: Number of subjects enrolled | Poland: 19              |
| Country: Number of subjects enrolled | Romania: 11             |
| Country: Number of subjects enrolled | Russian Federation: 131 |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Sweden: 16        |
| Country: Number of subjects enrolled | Turkey: 50        |
| Country: Number of subjects enrolled | Ukraine: 102      |
| Country: Number of subjects enrolled | United States: 92 |
| Worldwide total number of subjects   | 1052              |
| EEA total number of subjects         | 188               |

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)                      | 331 |
| From 65 to 84 years                       | 701 |
| 85 years and over                         | 20  |

## Subject disposition

### Recruitment

Recruitment details:

Response/progression or adverse events that occurred during a non-randomized switch-over to apalutamide+ADT were not counted towards efficacy or safety endpoints, respectively.

### Pre-assignment

Screening details:

Per protocol, 208 subjects randomized to receive placebo+ADT were switched over to receive apalutamide+ADT after interim analysis and unblinding. Randomized treatment disposition has been reported in subject disposition.

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Placebo + Androgen Deprivation Therapy (ADT) |

Arm description:

Subjects received matching placebo (4 tablets) orally once daily (qd) along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. In the event of a positive result at interim or final analysis subjects in treatment phase had opportunity to receive Apalutamide +ADT. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.

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

Dosage and administration details:

Subjects received matching placebo along with ADT orally once daily at pre-specified timepoints.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Apalutamide + ADT |
|------------------|-------------------|

Arm description:

Subjects received JNJ-56021927 (apalutamide) 240 milligrams (mg) (4\*60 mg tablets) orally qd along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Apalutamide  |
| Investigational medicinal product code |              |
| Other name                             | JNJ-56021927 |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects received apalutamide 240 mg (4\*60 mg) tablets orally along with ADT at pre-specified timepoints.

| <b>Number of subjects in period 1</b> | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT |
|---------------------------------------|--|-------------------|
| Started                               | 527  | 525               |
| Completed                             | 527  | 524               |
| Not completed                         | 0  | 1                 |
| Consent withdrawn by subject          | -  | 1                 |

## Period 2

|                              |                              |
|------------------------------|------------------------------|
| Period 2 title               | Treated                      |
| Is this the baseline period? | No                           |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

## Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Placebo + Androgen Deprivation Therapy (ADT) |

### Arm description:

Subjects received matching placebo (4 tablets) orally once daily (qd) along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. In the event of a positive result at interim or final analysis subjects in treatment phase had opportunity to receive Apalutamide +ADT. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.

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

### Dosage and administration details:

Subjects received matching placebo along with ADT orally once daily at pre-specified timepoints.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Apalutamide + ADT |
|------------------|-------------------|

### Arm description:

Subjects received JNJ-56021927 (apalutamide) 240 milligrams (mg) (4\*60 mg tablets) orally qd along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Apalutamide  |
| Investigational medicinal product code |              |
| Other name                             | JNJ-56021927 |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

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**Dosage and administration details:**

Subjects received apalutamide 240 mg (4\*60 mg) tablets orally along with ADT at pre-specified timepoints.

| <b>Number of subjects in period 2</b> | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT |
|---------------------------------------|--|-------------------|
|                                       |  |                   |
| Started                               | 527  | 524               |
| Completed                             | 208  | 0                 |
| Not completed                         | 319  | 524               |
| Adverse event, not serious            | 6  | 30                |
| Physician decision                    | 4  | 6                 |
| Consent withdrawn by subject          | 37   | 36                |
| Adverse event, non-fatal              | 8  | 18                |
| Death                                 | 18   | 25                |
| Other, progressive disease            | 245  | 138               |
| Unspecified                           | -  | 2                 |
| Other, ongoing                        | -  | 267               |
| Protocol deviation                    | 1  | 2                 |

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Placebo + Androgen Deprivation Therapy (ADT) |
| Reporting group description:  |  |
| Subjects received matching placebo (4 tablets) orally once daily (qd) along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. In the event of a positive result at interim or final analysis subjects in treatment phase had opportunity to receive Apalutamide +ADT. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death. |  |
| Reporting group title   | Apalutamide + ADT                            |
| Reporting group description:  |  |
| Subjects received JNJ-56021927 (apalutamide) 240 milligrams (mg) (4*60 mg tablets) orally qd along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.  |  |

| Reporting group values                      | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT | Total |
|---|--|-------------------|-------|
| Number of subjects                          | 527  | 525               | 1052  |
| Title for AgeCategorical<br>Units: subjects |  |                   |       |
| Children (2-11 years)                       | 0  | 0                 | 0     |
| Adolescents (12-17 years)                   | 0  | 0                 | 0     |
| Adults (18-64 years)                        | 182  | 149               | 331   |
| From 65 to 84 years                         | 335  | 366               | 701   |
| 85 years and over                           | 10   | 10                | 20    |
| Title for AgeContinuous<br>Units: years     |  |                   |       |
| arithmetic mean                             | 67.9   | 68.9              | -     |
| standard deviation                          | ± 8.42                                       | ± 8.11            | -     |
| Title for Gender<br>Units: subjects         |  |                   |       |
| Male  | 527  | 525               | 1052  |
| Region of Enrollment<br>Units: Subjects     |  |                   |       |
| Argentina                                   | 20   | 17                | 37    |
| Australia                                   | 5  | 6                 | 11    |
| Brazil                                      | 38   | 54                | 92    |
| Canada                                      | 16   | 14                | 30    |
| China                                       | 46   | 48                | 94    |
| Czech Republic                              | 12   | 19                | 31    |
| France                                      | 8  | 8                 | 16    |
| Germany                                     | 10   | 7                 | 17    |
| Hungary                                     | 11   | 13                | 24    |
| Israel                                      | 8  | 6                 | 14    |
| Italy                                       | 18   | 16                | 34    |
| Japan                                       | 23   | 28                | 51    |
| Mexico                                      | 25   | 23                | 48    |

|   |     |     |     |
|---|-----|-----|-----|
| Poland                                    | 12  | 7   | 19  |
| Romania                                   | 7   | 4   | 11  |
| Korea, Republic Of                        | 41  | 35  | 76  |
| Russia                                    | 66  | 65  | 131 |
| Spain                                     | 12  | 8   | 20  |
| Sweden                                    | 8   | 8   | 16  |
| Turkey                                    | 22  | 28  | 50  |
| Ukraine                                   | 60  | 42  | 102 |
| United States                             | 59  | 69  | 128 |
| Race (NIH/OMB)                            |     |     |     |
| Units: Subjects                           |     |     |     |
| American Indian or Alaska Native          | 11  | 6   | 17  |
| Asian                                     | 112 | 119 | 231 |
| Native Hawaiian or Other Pacific Islander | 0   | 0   | 0   |
| Black or African American                 | 9   | 10  | 19  |
| White                                     | 365 | 354 | 719 |
| More than one race                        | 0   | 1   | 1   |
| Unknown or Not Reported                   | 30  | 35  | 65  |



## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Placebo + Androgen Deprivation Therapy (ADT) |
| Reporting group description:<br>Subjects received matching placebo (4 tablets) orally once daily (qd) along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. In the event of a positive result at interim or final analysis subjects in treatment phase had opportunity to receive Apalutamide +ADT. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death. |  |
| Reporting group title   | Apalutamide + ADT                            |
| Reporting group description:<br>Subjects received JNJ-56021927 (apalutamide) 240 milligrams (mg) (4*60 mg tablets) orally qd along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.  |  |
| Reporting group title   | Placebo + Androgen Deprivation Therapy (ADT) |
| Reporting group description:<br>Subjects received matching placebo (4 tablets) orally once daily (qd) along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. In the event of a positive result at interim or final analysis subjects in treatment phase had opportunity to receive Apalutamide +ADT. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death. |  |
| Reporting group title   | Apalutamide + ADT                            |
| Reporting group description:<br>Subjects received JNJ-56021927 (apalutamide) 240 milligrams (mg) (4*60 mg tablets) orally qd along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.  |  |

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

|   |   |
|---|---|
| End point title   | Radiographic Progression-free Survival (rPFS) |
| End point description:<br>rPFS as assessed by the investigator was defined as the duration from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurred first. Radiographic progressive disease was defined as progression of soft tissue lesions measured by computed tomography (CT) or magnetic resonance imaging (MRI) as defined by modified Response evaluation criteria in solid tumors (RECIST) 1.1. Intent to treat (ITT) population included all randomized participants classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that the median, lower limit and upper limit of confidence interval (CI) were not estimable due to lesser number of events for Apalutamide + ADT arm. |   |
| End point type  | Primary                                       |
| End point timeframe:<br>Up to 35 months   |   |

| <b>End point values</b>          | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT      |  |  |
|----------------------------------|--|------------------------|--|--|
| Subject group type               | Reporting group                              | Reporting group        |  |  |
| Number of subjects analysed      | 527  | 525                    |  |  |
| Units: months                    |  |                        |  |  |
| median (confidence interval 95%) | 22.08 (18.46 to 32.92)                       | 99999 (99999 to 99999) |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1   |
|---|--|
| Comparison groups                       | Placebo + Androgen Deprivation Therapy (ADT) v Apalutamide + ADT |
| Number of subjects included in analysis | 1052   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.484  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.391  |
| upper limit                             | 0.6  |

## Primary: Overall Survival (OS)

|  |                       |
|--|-----------------------|
| End point title  | Overall Survival (OS) |
| End point description:   |                       |
| OS was defined as the time from date of randomization to date of death from any cause. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that the upper limit of CI was not estimable due to lesser number of events for Placebo + Androgen Deprivation Therapy [ADT] arm and the median, lower limit and upper limit of CI were not estimable due to lesser number of events for Apalutamide + ADT arm. |                       |
| End point type   | Primary               |
| End point timeframe:   |                       |
| Up to 57 months  |                       |

| <b>End point values</b>          | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT      |  |  |
|----------------------------------|--|------------------------|--|--|
| Subject group type               | Reporting group                              | Reporting group        |  |  |
| Number of subjects analysed      | 527  | 525                    |  |  |
| Units: months                    |  |                        |  |  |
| median (confidence interval 95%) | 52.17 (41.86 to 99999)                       | 99999 (99999 to 99999) |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1   |
|---|--|
| Comparison groups                       | Placebo + Androgen Deprivation Therapy (ADT) v Apalutamide + ADT |
| Number of subjects included in analysis | 1052   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.651  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.534  |
| upper limit                             | 0.793  |

## Secondary: Time to Initiation of Cytotoxic Chemotherapy

|  |  |
|--|--|
| End point title  | Time to Initiation of Cytotoxic Chemotherapy |
| End point description:   |  |
| Time to initiation of cytotoxic chemotherapy was defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that the median, lower limit and upper limit of CI were not estimable due to lesser number of events for both the arms. |  |
| End point type   | Secondary                                    |
| End point timeframe:   |  |
| Up to 57 months  |  |

| <b>End point values</b>     | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT |  |  |
|-----------------------------|--|-------------------|--|--|
| Subject group type          | Reporting group                              | Reporting group   |  |  |
| Number of subjects analysed | 527  | 525               |  |  |
| Units: months               |  |                   |  |  |

|                                  |                        |                        |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
|----------------------------------|------------------------|------------------------|--|--|

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1   |
| Comparison groups                       | Placebo + Androgen Deprivation Therapy (ADT) v Apalutamide + ADT |
| Number of subjects included in analysis | 1052   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.469  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.35   |
| upper limit                             | 0.63   |

## Secondary: Time to Pain Progression

|  |                          |
|--|--------------------------|
| End point title  | Time to Pain Progression |
| End point description:   |                          |
| Time to pain progression was defined as the time from the date of randomization to the date of the first observation of pain progression. Pain progression was defined as an average increase by 2 points from baseline to greater than (>) 4 on the Brief Pain Inventory-Short Form (BPI-SF) worst pain intensity (item 3) with no decrease in opioids confirmed greater than equal to (>=) 3 weeks apart or initiation of chronic opioids, whichever occurred first. BPI-SF is a self-administered questionnaire developed to assess severity of pain and impact of pain on daily functions. Item 3=worst pain intensity asks participants to rate worst pain in prior 7-days on a 0= No pain to 10=Pain as bad as you can imagine. A lower score is better. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that upper, lower limit of CI and median were not estimable due to lesser number of events. |                          |
| End point type   | Secondary                |
| End point timeframe:   |                          |
| Up to 57 months  |                          |

|                                  |  |                        |  |  |
|----------------------------------|--|------------------------|--|--|
| <b>End point values</b>          | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT      |  |  |
| Subject group type               | Reporting group                              | Reporting group        |  |  |
| Number of subjects analysed      | 527  | 525                    |  |  |
| Units: months                    |  |                        |  |  |
| median (confidence interval 95%) | 99999 (51.32 to 99999)                       | 99999 (99999 to 99999) |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1   |
| Comparison groups                       | Placebo + Androgen Deprivation Therapy (ADT) v Apalutamide + ADT |
| Number of subjects included in analysis | 1052   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.1966   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.868  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.7  |
| upper limit                             | 1.076  |

## Secondary: Time to Chronic Opioid Use

|  |                            |
|--|----------------------------|
| End point title  | Time to Chronic Opioid Use |
| End point description:<br>Time to chronic opioid use was defined as the time from date of randomization to the first date of confirmed chronic opioid use. For subjects entering the study without receiving opioids, chronic opioid use was defined as administration of opioid analgesics lasting for greater than or equal to ( $\geq$ ) 3 weeks for oral or $\geq$ 7 days for non-oral formulations. For participants entering study already receiving opioids, chronic opioid use was defined as a $\geq$ 30 percent (%) increase in total daily dose of the opioid analgesics lasting for $\geq$ 3 weeks for oral or $\geq$ 7 days for non-oral formulation. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that upper, lower limit of CI and median were not estimable due to lesser number of events. |                            |
| End point type   | Secondary                  |
| End point timeframe:<br>Up to 57 months  |                            |

|                                  |  |                        |  |  |
|----------------------------------|--|------------------------|--|--|
| <b>End point values</b>          | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT      |  |  |
| Subject group type               | Reporting group                              | Reporting group        |  |  |
| Number of subjects analysed      | 527  | 525                    |  |  |
| Units: months                    |  |                        |  |  |
| median (confidence interval 95%) | 99999 (51.32 to 99999)                       | 99999 (99999 to 99999) |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1   |
| Comparison groups                       | Placebo + Androgen Deprivation Therapy (ADT) v Apalutamide + ADT |
| Number of subjects included in analysis | 1052   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.1563   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.794  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.576  |
| upper limit                             | 1.094  |

## Secondary: Time to Skeletal-related Event (SRE)

|  |                                      |
|--|--------------------------------------|
| End point title  | Time to Skeletal-related Event (SRE) |
| End point description:   |                                      |
| Time to SRE was defined as the time from the date of randomization to the date of the first observation of an SRE. A SRE was defined as the occurrence of either a pathological fracture, or spinal cord compression, or radiation to bone, or surgery to bone. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "9999" signifies that the upper limit of CI was not estimable due to lesser number of events for Placebo + Androgen Deprivation Therapy [ADT] arm and the median, lower limit and upper limit of CI were not estimable due to lesser number of events for Apalutamide + ADT arm. |                                      |
| End point type   | Secondary                            |
| End point timeframe:   |                                      |
| Up to 57 months  |                                      |

| End point values                 | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT      |  |  |
|----------------------------------|--|------------------------|--|--|
| Subject group type               | Reporting group                              | Reporting group        |  |  |
| Number of subjects analysed      | 527  | 525                    |  |  |
| Units: months                    |  |                        |  |  |
| median (confidence interval 95%) | 99999 (51.78 to 99999)                       | 99999 (99999 to 99999) |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1   |
| Comparison groups                       | Placebo + Androgen Deprivation Therapy (ADT) v Apalutamide + ADT |
| Number of subjects included in analysis | 1052   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.3608   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.857  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.615  |
| upper limit                             | 1.194  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 57 months

Adverse event reporting additional description:

Safety Analysis set: All subjects who received at least 1 dose of randomized study drug. For crossover subjects, adverse events after initiation of crossover treatment were summarized separately in Placebo+ADT to Apalutamide+ADT arm. However, adverse events occurred before crossover treatment were summarized in Placebo+ADT arm.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo + Androgen Deprivation Therapy (ADT) |
|-----------------------|--|

Reporting group description:

Subjects received matching placebo (4 tablets) orally once daily (qd) along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. In the event of a positive result at interim or final analysis subjects in treatment phase had opportunity to receive Apalutamide +ADT. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Apalutamide + ADT |
|-----------------------|-------------------|

Reporting group description:

Subjects received JNJ-56021927 (apalutamide) 240 milligrams (mg) (4\*60 mg tablets) orally qd along with ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration) as standard of care therapy in each 28-day treatment cycle. The choice of the GnRHa (agonist or antagonist) was at discretion of the investigator. Subjects received treatment until radiographic progression or unequivocal clinical progression, unacceptable toxicity, or death.

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Placebo + ADT to Apalutamide + ADT |
|-----------------------|------------------------------------|

Reporting group description:

After interim analysis and unblinding, participants receiving placebo +ADT crossed over to receive 240 mg apalutamide orally qd along with ADT in open-label extension phase.

| Serious adverse events  | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT  | Placebo + ADT to Apalutamide + ADT |
|---|--|--------------------|------------------------------------|
| Total subjects affected by serious adverse events                   |  |                    |                                    |
| subjects affected / exposed   | 115 / 527 (21.82%)                           | 153 / 524 (29.20%) | 29 / 208 (13.94%)                  |
| number of deaths (all causes)                                       | 35   | 31                 | 10                                 |
| number of deaths resulting from adverse events                      |  |                    |                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                    |                                    |
| Adenocarcinoma of Colon   |  |                    |                                    |
| subjects affected / exposed   | 0 / 527 (0.00%)                              | 2 / 524 (0.38%)    | 0 / 208 (0.00%)                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 2              | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0              | 0 / 0                              |
| Adrenal Neoplasm  |  |                    |                                    |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Benign Lung Neoplasm                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder Cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Burkitt's Lymphoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cancer Pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric Cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leiomyosarcoma                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung Carcinoma Cell Type Unspecified Stage I    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung Neoplasm Malignant                         |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 527 (0.19%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningioma   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to Central Nervous System                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-Small Cell Lung Cancer                           |                 |                 |                 |
| subjects affected / exposed                          | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory Papilloma                                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Squamous Cell Carcinoma                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Deep Vein Thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 527 (0.00%) | 3 / 524 (0.57%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Asthenia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Exercise Tolerance Decreased                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fatigue   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 527 (0.57%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gait Disturbance                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| General Physical Health Deterioration           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-Cardiac Chest Pain                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 2 / 208 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oedema  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Performance Status Decreased                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral Swelling                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Benign Prostatic Hyperplasia                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 2 / 524 (0.38%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute Pulmonary Oedema                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute Respiratory Failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic Obstructive Pulmonary Disease           |                 |                 |                 |
| subjects affected / exposed                     | 3 / 527 (0.57%) | 3 / 524 (0.57%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 6           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydrothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Organising Pneumonia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Paranasal Cyst                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural Effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleuritic Pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax Spontaneous                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary Embolism                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary Haemorrhage                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary Mass                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary Oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory Failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%) | 2 / 208 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Confusional State                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mental Status Changes                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicidal Ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicide Attempt                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Product issues                                  |                 |                 |                 |
| Device Malfunction                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| International Normalised Ratio Increased        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight Decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Acetabulum Fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankle Fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain Contusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clavicle Fracture                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Comminuted Fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral Neck Fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur Fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Forearm Fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hand Fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip Fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incisional Hernia                               |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ligament Sprain                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower Limb Fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Patella Fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Radius Fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib Fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skull Fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Soft Tissue Injury                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal Compression Fracture                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 4 / 524 (0.76%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid Haematoma                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural Haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural Haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thoracic Vertebral Fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tibia Fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Traumatic Fracture                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute Coronary Syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute Myocardial Infarction                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina Pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina Unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic Valve Disease Mixed                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriosclerosis Coronary Artery                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial Fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular Block Complete                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac Amyloidosis                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac Disorder                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac Failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac Failure Chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac Failure Congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cor Pulmonale Chronic                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary Artery Occlusion                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary Artery Stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 3 / 524 (0.57%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral Valve Disease                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial Infarction                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 8 / 524 (1.53%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 9           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial Ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinoatrial Block                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus Node Dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular Extrasystoles                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular Tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular Fibrillation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Cauda Equina Syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral Haemorrhage                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular Accident                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 4 / 524 (0.76%) | 3 / 208 (1.44%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cognitive Disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diplegia  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhage Intracranial                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydrocephalus                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Iiird Nerve Paresis                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic Stroke                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Migraine  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Paraplegia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seizure   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal Cord Compression                         |                 |                 |                 |
| subjects affected / exposed                     | 6 / 527 (1.14%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid Haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 6 / 527 (1.14%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coagulopathy                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Febrile Neutropenia                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo Positional                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Cataract  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Open Angle Glaucoma                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal Distension                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal Pain Lower                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Anal Fistula                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyschezia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric Ulcer Perforation                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal Haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic Erosive Gastritis                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal Hernia                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large Intestinal Ulcer Perforation              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large Intestine Polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Proctalgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Terminal Ileitis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Bile Duct Stone                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholangitis Acute                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis Acute                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic Cirrhosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic Failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Jaundice  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Drug Eruption                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rash  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| Acute Kidney Injury                             |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Bladder Perforation                             |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Bladder Tamponade                               |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Calculus Bladder                                |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Calculus Urinary                                |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Dysuria   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Haematuria                                      |                 |                  |                 |
| subjects affected / exposed                     | 3 / 527 (0.57%) | 10 / 524 (1.91%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 13           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Hydronephrosis                                  |                 |                  |                 |
| subjects affected / exposed                     | 4 / 527 (0.76%) | 2 / 524 (0.38%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Nephrolithiasis                                 |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal Disorder                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal Failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ureteric Obstruction                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ureterolithiasis                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urethral Stenosis                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary Bladder Haematoma                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary Retention                               |                 |                 |                 |
| subjects affected / exposed                     | 9 / 527 (1.71%) | 4 / 524 (0.76%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary Tract Obstruction                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                 |                 |                 |
| Goitre  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperparathyroidism                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 4 / 524 (0.76%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Back Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 6 / 527 (1.14%) | 4 / 524 (0.76%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bone Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 2 / 208 (0.96%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral Disc Protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Lumbar Spinal Stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscular Weakness                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal Pain                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myalgia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 527 (0.76%) | 1 / 524 (0.19%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteonecrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in Extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pathological Fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 4 / 527 (0.76%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rheumatoid Arthritis                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rotator Cuff Syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal Abscess                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abscess Jaw                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abscess Oral                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchiolitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 3 / 524 (0.57%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis Infective                         |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium Difficile Colitis                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fournier's Gangrene                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infected Lymphocele                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Kidney Infection                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Klebsiella Infection                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Localised Infection                             |                 |                 |                 |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Lower Respiratory Tract Infection               |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Muscle Abscess                                  |                 |                  |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Peritonitis                                     |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pneumonia                                       |                 |                  |                 |
| subjects affected / exposed                     | 3 / 527 (0.57%) | 10 / 524 (1.91%) | 3 / 208 (1.44%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 13           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pneumonia Bacterial                             |                 |                  |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pulmonary Tuberculosis                          |                 |                  |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pyelonephritis Acute                            |                 |                  |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 2 / 524 (0.38%)  | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Sepsis  |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 2 / 208 (0.96%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic Shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Staphylococcal Infection                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper Respiratory Tract Infection               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary Tract Infection                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 5 / 524 (0.95%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 5 / 524 (0.95%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral Infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral Upper Respiratory Tract Infection         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |                 |
| <b>Dehydration</b>                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 0 / 524 (0.00%) | 1 / 208 (0.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Diabetes Mellitus</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 3 / 524 (0.57%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Diabetes Mellitus Inadequate Control</b>     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypercalcaemia</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 527 (0.00%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hyperglycaemia</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 2 / 524 (0.38%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypokalaemia</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 527 (0.19%) | 1 / 524 (0.19%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hyponatraemia</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 527 (0.38%) | 0 / 524 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                           | Placebo + Androgen Deprivation Therapy (ADT) | Apalutamide + ADT  | Placebo + ADT to Apalutamide + ADT |
|---|--|--------------------|------------------------------------|
| Total subjects affected by non-serious adverse events       |  |                    |                                    |
| subjects affected / exposed                                 | 472 / 527 (89.56%)                           | 469 / 524 (89.50%) | 136 / 208 (65.38%)                 |
| <b>Vascular disorders</b>                                   |  |                    |                                    |
| Hot Flush   |  |                    |                                    |
| subjects affected / exposed                                 | 87 / 527 (16.51%)                            | 121 / 524 (23.09%) | 3 / 208 (1.44%)                    |
| occurrences (all)   | 96   | 136                | 3                                  |
| Hypertension  |  |                    |                                    |
| subjects affected / exposed                                 | 84 / 527 (15.94%)                            | 100 / 524 (19.08%) | 13 / 208 (6.25%)                   |
| occurrences (all)   | 153  | 200                | 16                                 |
| <b>General disorders and administration site conditions</b> |  |                    |                                    |
| Asthenia  |  |                    |                                    |
| subjects affected / exposed                                 | 45 / 527 (8.54%)                             | 40 / 524 (7.63%)   | 8 / 208 (3.85%)                    |
| occurrences (all)   | 63   | 54                 | 9                                  |
| Fatigue   |  |                    |                                    |
| subjects affected / exposed                                 | 87 / 527 (16.51%)                            | 107 / 524 (20.42%) | 15 / 208 (7.21%)                   |
| occurrences (all)   | 97   | 144                | 20                                 |
| Oedema Peripheral   |  |                    |                                    |
| subjects affected / exposed                                 | 41 / 527 (7.78%)                             | 32 / 524 (6.11%)   | 4 / 208 (1.92%)                    |
| occurrences (all)   | 50   | 45                 | 4                                  |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |  |                    |                                    |
| Cough   |  |                    |                                    |
| subjects affected / exposed                                 | 33 / 527 (6.26%)                             | 40 / 524 (7.63%)   | 4 / 208 (1.92%)                    |
| occurrences (all)   | 37   | 46                 | 5                                  |
| <b>Psychiatric disorders</b>                                |  |                    |                                    |
| Insomnia  |  |                    |                                    |
| subjects affected / exposed                                 | 33 / 527 (6.26%)                             | 28 / 524 (5.34%)   | 5 / 208 (2.40%)                    |
| occurrences (all)   | 35   | 37                 | 5                                  |
| <b>Investigations</b>                                       |  |                    |                                    |
| Alanine Aminotransferase Increased                          |  |                    |                                    |
| subjects affected / exposed                                 | 42 / 527 (7.97%)                             | 25 / 524 (4.77%)   | 4 / 208 (1.92%)                    |
| occurrences (all)   | 71   | 33                 | 5                                  |
| Aspartate Aminotransferase Increased                        |  |                    |                                    |

|  |                   |                   |                  |
|--|-------------------|-------------------|------------------|
| subjects affected / exposed                    | 43 / 527 (8.16%)  | 18 / 524 (3.44%)  | 5 / 208 (2.40%)  |
| occurrences (all)                              | 71                | 26                | 7                |
| Blood Alkaline Phosphatase Increased           |                   |                   |                  |
| subjects affected / exposed                    | 32 / 527 (6.07%)  | 18 / 524 (3.44%)  | 3 / 208 (1.44%)  |
| occurrences (all)                              | 54                | 28                | 6                |
| Weight Decreased                               |                   |                   |                  |
| subjects affected / exposed                    | 29 / 527 (5.50%)  | 43 / 524 (8.21%)  | 9 / 208 (4.33%)  |
| occurrences (all)                              | 39                | 66                | 11               |
| Weight Increased                               |                   |                   |                  |
| subjects affected / exposed                    | 92 / 527 (17.46%) | 55 / 524 (10.50%) | 7 / 208 (3.37%)  |
| occurrences (all)                              | 143               | 86                | 8                |
| Injury, poisoning and procedural complications |                   |                   |                  |
| Fall   |                   |                   |                  |
| subjects affected / exposed                    | 36 / 527 (6.83%)  | 47 / 524 (8.97%)  | 8 / 208 (3.85%)  |
| occurrences (all)                              | 53                | 59                | 14               |
| Nervous system disorders                       |                   |                   |                  |
| Dizziness                                      |                   |                   |                  |
| subjects affected / exposed                    | 35 / 527 (6.64%)  | 24 / 524 (4.58%)  | 7 / 208 (3.37%)  |
| occurrences (all)                              | 43                | 34                | 7                |
| Headache                                       |                   |                   |                  |
| subjects affected / exposed                    | 31 / 527 (5.88%)  | 44 / 524 (8.40%)  | 12 / 208 (5.77%) |
| occurrences (all)                              | 46                | 59                | 14               |
| Blood and lymphatic system disorders           |                   |                   |                  |
| Anaemia  |                   |                   |                  |
| subjects affected / exposed                    | 71 / 527 (13.47%) | 68 / 524 (12.98%) | 13 / 208 (6.25%) |
| occurrences (all)                              | 125               | 95                | 18               |
| Leukopenia                                     |                   |                   |                  |
| subjects affected / exposed                    | 21 / 527 (3.98%)  | 29 / 524 (5.53%)  | 8 / 208 (3.85%)  |
| occurrences (all)                              | 35                | 54                | 11               |
| Gastrointestinal disorders                     |                   |                   |                  |
| Constipation                                   |                   |                   |                  |
| subjects affected / exposed                    | 57 / 527 (10.82%) | 58 / 524 (11.07%) | 6 / 208 (2.88%)  |
| occurrences (all)                              | 72                | 68                | 8                |
| Diarrhoea                                      |                   |                   |                  |
| subjects affected / exposed                    | 35 / 527 (6.64%)  | 56 / 524 (10.69%) | 11 / 208 (5.29%) |
| occurrences (all)                              | 43                | 71                | 16               |

|   |                           |                           |                         |
|---|---------------------------|---------------------------|-------------------------|
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 44 / 527 (8.35%)<br>55    | 41 / 524 (7.82%)<br>52    | 12 / 208 (5.77%)<br>14  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 25 / 527 (4.74%)<br>30    | 58 / 524 (11.07%)<br>73   | 13 / 208 (6.25%)<br>14  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 23 / 527 (4.36%)<br>31    | 106 / 524 (20.23%)<br>202 | 26 / 208 (12.50%)<br>42 |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                        | 30 / 527 (5.69%)<br>36    | 35 / 524 (6.68%)<br>40    | 3 / 208 (1.44%)<br>3    |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 82 / 527 (15.56%)<br>110  | 101 / 524 (19.27%)<br>133 | 15 / 208 (7.21%)<br>17  |
| Back Pain<br>subjects affected / exposed<br>occurrences (all)   | 108 / 527 (20.49%)<br>144 | 106 / 524 (20.23%)<br>151 | 11 / 208 (5.29%)<br>14  |
| Bone Pain<br>subjects affected / exposed<br>occurrences (all)   | 53 / 527 (10.06%)<br>75   | 39 / 524 (7.44%)<br>54    | 0 / 208 (0.00%)<br>0    |
| Musculoskeletal Pain<br>subjects affected / exposed<br>occurrences (all)  | 41 / 527 (7.78%)<br>52    | 39 / 524 (7.44%)<br>59    | 5 / 208 (2.40%)<br>5    |
| Pain in Extremity<br>subjects affected / exposed<br>occurrences (all)   | 67 / 527 (12.71%)<br>93   | 69 / 524 (13.17%)<br>91   | 8 / 208 (3.85%)<br>8    |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                | 47 / 527 (8.92%)<br>62    | 44 / 524 (8.40%)<br>73    | 6 / 208 (2.88%)<br>8    |
| Upper Respiratory Tract Infection   |                           |                           |                         |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                            | 29 / 527 (5.50%)<br>46 | 40 / 524 (7.63%)<br>46 | 6 / 208 (2.88%)<br>7   |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 22 / 527 (4.17%)<br>31 | 28 / 524 (5.34%)<br>47 | 4 / 208 (1.92%)<br>5   |
| Metabolism and nutrition disorders  |                        |                        |                        |
| Decreased Appetite<br>subjects affected / exposed<br>occurrences (all)      | 27 / 527 (5.12%)<br>32 | 32 / 524 (6.11%)<br>38 | 11 / 208 (5.29%)<br>12 |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 527 (1.52%)<br>8   | 34 / 524 (6.49%)<br>37 | 7 / 208 (3.37%)<br>7   |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)           | 27 / 527 (5.12%)<br>40 | 47 / 524 (8.97%)<br>87 | 16 / 208 (7.69%)<br>23 |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 08 April 2016     | Inclusion criteria were amended based on feedback from investigators or steering committee members: inclusion criterion 2 added subjects with high-volume metastatic castration sensitive, prostate cancer (mCSPC) and removed the requirement for histologic evidence of prostate adenocarcinoma from a metastatic lesion for subjects who had been diagnosed more than 5 years prior to randomization, inclusion criterion 3 was changed to allow a single bone lesion on bone scan, inclusion criterion 4 restricted Eastern Cooperative Oncology Group (ECOG) performance status to grade 0 or 1 (removed eligibility for grade 2), exclusion criterion 8 clarified that bisphosphonates and denosumab for the management of bone metastasis are not allowed, exclusion criterion 10 incorporated blood product and growth factor support. Criteria for prior prostate cancer therapy were modified based on Steering Committee feedback. Collection of trough pharmacokinetic samples became mandatory, clarified collection (voluntary) and volume (4 mL) of PK samples for leuprolide study, and removed collection of circulating tumor cells, Local amendments to Japan and the Czech Republic were incorporated. |
| 02 February 2017  | Pharmacokinetic (PK) sub-study for leuprolide amended to allow leuprolide doses of 11.25 milligrams (mg), 22.5 mg, 30 mg, and 45 mg administered by subcutaneous or intramuscular route. Description of analysis of dual primary endpoints revised to clarify that subgroup analysis by volume of disease will be performed for both endpoints ( radiographic progression free survival [rPFS] and OS). Clarification that timing for the interim analysis of OS and final analysis of rPFS may not be in alignment if the number of death events for the interim analysis of OS would require an extended delay in the analysis of the rPFS endpoint.   |
| 22 February 2018  | Open-label Extension Phase revised to include information and details for the crossover to open-label apalutamide after study unblinding, such as details on the Cross-over Eligibility Phase, timing of patient-reported outcomes and biomarker collection, information on collection of additional endpoints, timing of serum chemistry and hematology sampling. Interim analysis was revised to occur at approximately 60% of events (previously 50%), due to external data relating to study population.   |
| 05 September 2018 | The 2 interim analyses planned for this study were changed to observing approximately 50 percent (%) (previously 60%) and 70% (previously 75%) of the total number of required (410) OS events, based on lower number of overall survival (OS) events and on recent data from a Phase 3 apalutamide clinical study. Updates were made to restricted concomitant medications based on the latest available information on the potential for drug interactions with apalutamide.   |
| 16 March 2020     | A Long-term Extension (LTE) Phase was added to the protocol to allow subjects to continue to derive benefit from treatment (based on investigator assessment). A brief description of the LTE Phase was added to the main body and a detailed section was added as an attachment.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported