



## Clinical trial results:

**VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of 177Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)**

### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2018-000459-41       |
| Trial protocol           | GB DE SE FR DK NL BE |
| Global end of trial date | 14 December 2023     |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 28 December 2024 |
| First version publication date | 28 December 2024 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | PSMA-617-01 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                         |
|------------------------------------|-------------------------|
| ISRCTN number                      | -                       |
| ClinicalTrials.gov id (NCT number) | NCT03511664             |
| WHO universal trial number (UTN)   | -                       |
| Other trial identifiers            | Novartis: CAAA617A12301 |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 14 December 2023 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 December 2023 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the two alternate primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who received 177Lu-PSMA-617 in addition to best supportive/best standard of care (BSC/BSoC) versus patients treated with best supportive/best standard of care alone.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 29 May 2018 |
| 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 | Belgium: 17        |
| Country: Number of subjects enrolled | Canada: 49         |
| Country: Number of subjects enrolled | Denmark: 24        |
| Country: Number of subjects enrolled | France: 70         |
| Country: Number of subjects enrolled | Netherlands: 38    |
| Country: Number of subjects enrolled | Sweden: 33         |
| Country: Number of subjects enrolled | United Kingdom: 47 |
| Country: Number of subjects enrolled | United States: 553 |
| Country: Number of subjects enrolled | Germany: 30        |
| Worldwide total number of subjects   | 861                |
| EEA total number of subjects         | 212                |

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|   |     |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 217 |
| From 65 to 84 years                       | 630 |
| 85 years and over                         | 14  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 86 sites across 9 countries. Belgium (3); Canada (7); Denmark (3); France (6); Netherlands (4); Sweden (5); UK (9); US (45); Germany (4, for the sub-study only)

### Pre-assignment

Screening details:

Screening period of up to 28 days before starting randomized treatment.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

Blinding implementation details:

Participants in the Main Study were randomized in a 2:1 ratio to receive either 177Lu-PSMA-617 plus BSC/BSOC or BSC/BSOC only. The sub-study was conducted in a non-randomized cohort (AAA617+ BSC/BSOC)

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| <b>Arm title</b>             | Main Study: 177Lu-PSMA-617 + BS/BSOC |

Arm description:

Patients randomized to receive the investigational product received 7.4 GBq (+/- 10%) 177Lu-PSMA-617 intravenously every 6 weeks (+/- 1 week) for a maximum of 6 cycles. Best supportive/best standard of care (BS/BSOC) might be used

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Best supportive/best standard of care                                   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for injection, Tablet, Radiopharmaceutical precursor, solution |
| Routes of administration               | Intravenous use, Oral use, Other use                                    |

Dosage and administration details:

Best supportive/best standard of care as defined by the local investigator

|  |                        |
|--|------------------------|
| Investigational medicinal product name | 177Lu-PSMA-617         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Administered intravenously once every 6 weeks (1 cycle) for a maximum of 6 cycles. After 4 cycles, patients were assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to 177Lu-PSMA-617. If all 3 assessments were met the patient might received an additional 2 cycles of 177Lu-PSMA-617.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Main Study: BS/BSOC alone |
|------------------|---------------------------|

Arm description:

Patients randomized to this arm received best supportive/best standard of care (BS/BSOC) as determined by the investigator

|          |                                       |
|----------|---------------------------------------|
| Arm type | Best supportive/best standard of care |
|----------|---------------------------------------|

|   |   |
|---|---|
| Investigational medicinal product name  | Best supportive/best standard of care                                   |
| Investigational medicinal product code  |   |
| Other name  |   |
| Pharmaceutical forms  | Solution for injection, Tablet, Radiopharmaceutical precursor, solution |
| Routes of administration  | Intravenous use, Oral use, Other use                                    |
| Dosage and administration details:  |   |
| Best supportive/best standard of care as defined by the local investigator  |   |
| <b>Arm title</b>  | Sub Study: 177Lu-PSMA-617 + BS/BSOC                                     |
| Arm description:  |   |
| non-randomized cohort (AAA617+ BSC/BSOC) at sites in Germany to provide a more complete assessment of the safety aspects of AAA617. Patients were treated and followed up similarly to the AAA617+BSC/BSOC (investigational arm) patients in the main study |   |
| Arm type  | Experimental  |
| Investigational medicinal product name  | Best supportive/best standard of care                                   |
| Investigational medicinal product code  |   |
| Other name  |   |
| Pharmaceutical forms  | Solution for injection, Tablet, Radiopharmaceutical precursor, solution |
| Routes of administration  | Intravenous use, Oral use, Other use                                    |
| Dosage and administration details:  |   |
| Best supportive/best standard of care as defined by the local investigator  |   |
| Investigational medicinal product name  | 177Lu-PSMA-617  |
| Investigational medicinal product code  |   |
| Other name  |   |
| Pharmaceutical forms  | Solution for injection  |
| Routes of administration  | Intravenous use   |

Dosage and administration details:

Administered intravenously once every 6 weeks (1 cycle) for a maximum of 6 cycles. After 4 cycles, patients were assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to 177Lu-PSMA-617. If all 3 assessments were met the patient might received an additional 2 cycles of 177Lu-PSMA-617.

| Number of subjects in period 1               | Main Study: 177Lu-PSMA-617 + BS/BSOC | Main Study: BS/BSOC alone | Sub Study: 177Lu-PSMA-617 + BS/BSOC |
|--|--------------------------------------|---------------------------|-------------------------------------|
|  |                                      |                           |                                     |
| Started                                      | 551                                  | 280                       | 30                                  |
| FAS Safety Analysis Set                      | 529                                  | 205                       | 30                                  |
| PFS-FAS Analysis Set                         | 385                                  | 196                       | 0 <sup>[1]</sup>                    |
| Response Evaluable Analysis Set              | 319                                  | 120                       | 0 <sup>[2]</sup>                    |
| Completed                                    | 28                                   | 6                         | 4                                   |
| Not completed                                | 523                                  | 274                       | 26                                  |
| Adverse event, serious fatal                 | 457                                  | 201                       | 21                                  |
| Physician decision                           | 2                                    | 1                         | -                                   |
| Other protocol pre-specified reasons for d/c | 15                                   | 4                         | 2                                   |
| Patient non-compliance                       | 1                                    | -                         | -                                   |
| Lost to follow-up                            | 8                                    | 5                         | -                                   |
| Withdrew consent                             | 40                                   | 63                        | 3                                   |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only apply to the Main Study

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only apply to the Main Study

## Baseline characteristics

### Reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | Main Study: 177Lu-PSMA-617 + BS/BSOC |
| Reporting group description:  |                                      |
| Patients randomized to receive the investigational product received 7.4 GBq (+/- 10%) 177Lu-PSMA-617 intravenously every 6 weeks (+/- 1 week) for a maximum of 6 cycles. Best supportive/best standard of care (BS/BSOC) might be used                      |                                      |
| Reporting group title   | Main Study: BS/BSOC alone            |
| Reporting group description:  |                                      |
| Patients randomized to this arm received best supportive/best standard of care (BS/BSOC) as determined by the investigator  |                                      |
| Reporting group title   | Sub Study: 177Lu-PSMA-617 + BS/BSOC  |
| Reporting group description:  |                                      |
| non-randomized cohort (AAA617+ BSC/BSOC) at sites in Germany to provide a more complete assessment of the safety aspects of AAA617. Patients were treated and followed up similarly to the AAA617+BSC/BSOC (investigational arm) patients in the main study |                                      |

| Reporting group values   | Main Study: 177Lu-PSMA-617 + BS/BSOC | Main Study: BS/BSOC alone | Sub Study: 177Lu-PSMA-617 + BS/BSOC |
|--|--------------------------------------|---------------------------|-------------------------------------|
| Number of subjects   | 551                                  | 280                       | 30                                  |
| Age Categorical  |                                      |                           |                                     |
| Units: Participants  |                                      |                           |                                     |
| < 65 years   | 145                                  | 60                        | 12                                  |
| ≥ 65-84 years  | 398                                  | 214                       | 18                                  |
| ≥ 85 years   | 8                                    | 6                         | 0                                   |
| Sex: Female, Male  |                                      |                           |                                     |
| Units: Participants  |                                      |                           |                                     |
| Female   | 0                                    | 0                         | 0                                   |
| Male   | 551                                  | 280                       | 30                                  |
| Race/Ethnicity, Customized   |                                      |                           |                                     |
| Race 'Other' included Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native and more than one race reported. |                                      |                           |                                     |
| Units: Subjects  |                                      |                           |                                     |
| White  | 486                                  | 235                       | 30                                  |
| Black or African American  | 34                                   | 21                        | 0                                   |
| Asian  | 9                                    | 11                        | 0                                   |
| Other  | 2                                    | 0                         | 0                                   |
| Missing  | 20                                   | 13                        | 0                                   |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 861   |  |  |
| Age Categorical        |       |  |  |
| Units: Participants    |       |  |  |
| < 65 years             | 217   |  |  |
| ≥ 65-84 years          | 630   |  |  |
| ≥ 85 years             | 14    |  |  |
| Sex: Female, Male      |       |  |  |
| Units: Participants    |       |  |  |
| Female                 | 0     |  |  |

|      |     |  |  |
|------|-----|--|--|
| Male | 861 |  |  |
|------|-----|--|--|

|  |     |  |  |
|--|-----|--|--|
| Race/Ethnicity, Customized   |     |  |  |
| Race 'Other' included Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native and more than one race reported. |     |  |  |
| Units: Subjects  |     |  |  |
| White  | 751 |  |  |
| Black or African American  | 55  |  |  |
| Asian  | 20  |  |  |
| Other  | 2   |  |  |
| Missing  | 33  |  |  |



## End points

### End points reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | Main Study: 177Lu-PSMA-617 + BS/BSOC |
| Reporting group description:<br>Patients randomized to receive the investigational product received 7.4 GBq (+/- 10%) 177Lu-PSMA-617 intravenously every 6 weeks (+/- 1 week) for a maximum of 6 cycles. Best supportive/best standard of care (BS/BSOC) might be used                      |                                      |
| Reporting group title   | Main Study: BS/BSOC alone            |
| Reporting group description:<br>Patients randomized to this arm received best supportive/best standard of care (BS/BSOC) as determined by the investigator  |                                      |
| Reporting group title   | Sub Study: 177Lu-PSMA-617 + BS/BSOC  |
| Reporting group description:<br>non-randomized cohort (AAA617+ BSC/BSOC) at sites in Germany to provide a more complete assessment of the safety aspects of AAA617. Patients were treated and followed up similarly to the AAA617+BSC/BSOC (investigational arm) patients in the main study |                                      |

### Primary: Overall Survival (OS)

|  |                                      |
|--|--------------------------------------|
| End point title  | Overall Survival (OS) <sup>[1]</sup> |
| End point description:<br>Overall Survival (OS) was defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient was not known to have died, then OS was censored. The censoring date was date of the last study visit, or contact, until the cut-off date. The cut-off date was not used for last contact date, unless the patient was seen or contacted on that date.<br>Final OS was analyzed at the time of Primary analysis (Primary Analysis cut-off date = 27-Jan-2021) and an updated descriptive analysis of OS was re-run at the time of final analysis (Final Analysis cut-off date 14-Dec-2023). |                                      |
| End point type   | Primary                              |
| End point timeframe:<br>From date of randomization until date of death from any cause, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021) and up to 66 months (Final Analysis cut-off date = 14-Dec-2023)  |                                      |

#### Notes:

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

| End point values                 | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 551  | 280                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) |  |                              |  |  |
| Primary OS Analysis              | 15.3 (14.2 to 16.9)                            | 11.3 (9.8 to 13.5)           |  |  |
| Final OS analysis                | 15.3 (14.2 to 16.9)                            | 11.5 (9.9 to 13.5)           |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Final OS analysis  |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 831  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| Parameter estimate                      | Cox proportional hazard  |
| Point estimate                          | 0.68   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.58   |
| upper limit                             | 0.81   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Primary OS Analysis  |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 831  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.62   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.52   |
| upper limit                             | 0.74   |

### Primary: Radiographic progression-free survival (rPFS)

|                        |   |
|------------------------|---|
| End point title        | Radiographic progression-free survival (rPFS) <sup>[2]</sup>  |
| End point description: | <p>Radiographic progression-free survival (rPFS) was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on the central review assessment per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria or death due to any cause. Patients who were alive without radiographic progression at the analysis data cut-off were censored for rPFS at the time of their last evaluable radiographic assessment. Date of censoring for rPFS: 1) The censoring date was the date when the last evaluable radiographic assessment (CT/MRI/bone scan) determined a lack of progression; 2) If there were no evaluable assessments, censoring occurred at the date of randomization; 3) Patients who had 2 or more consecutive missed tumor assessments immediately prior to PD or death were censored at the date of the last evaluable tumor assessment prior to those missing tumor assessments.</p> |
| End point type         | Primary   |
| End point timeframe:   | <p>From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)</p>   |

Notes:

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

|                                    |  |                              |  |  |
|------------------------------------|--|------------------------------|--|--|
| <b>End point values</b>            | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type                 | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed        | 385  | 196                          |  |  |
| Units: Months                      |  |                              |  |  |
| median (confidence interval 99.2%) | 8.7 (7.9 to<br>10.8)                           | 3.4 (2.4 to 4.0)             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Radiographic progression-free survival (rPFS)                    |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 581  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.4  |
| Confidence interval                     |  |
| level                                   | Other: 99.2 %  |
| sides                                   | 2-sided  |
| lower limit                             | 0.29   |
| upper limit                             | 0.57   |

## Secondary: Number of participants with randomized/study treatment-emergent adverse events (TEAE)

|                 |   |
|-----------------|---|
| End point title | Number of participants with randomized/study treatment-emergent adverse events (TEAE) |
|-----------------|---|

End point description:

In the Main Study, "randomized treatment" refers to the investigational arm (AAA617+BSC/BSoC) and the control arm (BSC/BSoC). In the sub-study, "study treatment" refers to the investigational arm (AAA617+BSC/BSoC) without randomization:

- 1) A randomized treatment-emergent adverse event (TEAE) is any adverse event that occurs from the start of randomized treatment to 30 days after the last administration of randomized treatment or prior to the initiation of subsequent anticancer treatment.
- 2) A study treatment-emergent adverse event (TEAE) is any adverse event that occurs from the start of study treatment to 30 days after the last administration of study treatment or prior to the initiation of subsequent anticancer treatment.

The distribution of randomized/study treatment-emergent adverse events (TEAEs) was done via the analysis of frequencies for TEAEs and Serious Adverse Event (TESAEs), through the monitoring of relevant clinical and laboratory safety parameters.

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

End point timeframe:

From randomization till 30 days safety follow-up, assessed up to 66 months (Final Analysis cut-off date = 14-Dec-2023)

| End point values                                     | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone | Sub Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC |  |
|--|--|------------------------------|---|--|
| Subject group type                                   | Reporting group                                | Reporting group              | Reporting group                               |  |
| Number of subjects analysed                          | 529  | 205                          | 30  |  |
| Units: Participants                                  |  |                              |   |  |
| TEAE   | 518  | 170                          | 30  |  |
| Serious TEAE   | 195  | 58                           | 9   |  |
| Grade 3/4/5 TEAE                                     | 284  | 79                           | 11  |  |
| Drug-related TEAE                                    | 451  | 59                           | 19  |  |
| Serious Drug-related TEAE                            | 51   | 5                            | 2   |  |
| Drug-related grade 3/4/5 TEAE                        | 152  | 8                            | 6   |  |
| TEAE leading to reduction of 177Lu-<br>PSMA-617      | 30   | 0                            | 2   |  |
| TEAE leading to reduction of BSC/BSOC                | 17   | 7                            | 1   |  |
| TEAE leading to interruption of 177Lu-<br>PSMA-617   | 85   | 2                            | 4   |  |
| TEAE leading to interruption of<br>BSC/BSOC          | 50   | 14                           | 1   |  |
| TEAE leading to discontinuation of<br>177Lu-PSMA-617 | 63   | 1                            | 2   |  |
| TEAE leading to discontinuation of<br>BSC/BSOC       | 47   | 16                           | 0   |  |
| Fatal TEAE   | 19   | 6                            | 2   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate (ORR)

|  |  |
|--|--|
| End point title  | Overall Response Rate (ORR) <sup>[3]</sup> |
| End point description:   |  |
| Overall Response Rate (ORR) was defined as the proportion of participants with Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR). ORR was based on RECIST 1.1 response for patients with evaluable disease at baseline per central review assessment. |  |
| End point type   | Secondary                                  |

End point timeframe:

From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

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

|                             |  |                              |  |  |
|-----------------------------|--|------------------------------|--|--|
| <b>End point values</b>     | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type          | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed | 319  | 120                          |  |  |
| Units: Participants         | 95   | 2                            |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Overall Response Rate (ORR)                                      |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 439  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 24.99  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 6.05   |
| upper limit                             | 103.24   |

## Secondary: Disease control rate (DCR)

|                        |   |
|------------------------|---|
| End point title        | Disease control rate (DCR) <sup>[4]</sup>   |
| End point description: |   |
|                        | Disease control rate (DCR) was defined as the proportion of participants with Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) or Stable Disease (SD) according to RECIST v1.1 per central review assessment. |
| End point type         | Secondary   |

### End point timeframe:

From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

### Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

|                             |  |                              |  |  |
|-----------------------------|--|------------------------------|--|--|
| <b>End point values</b>     | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type          | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed | 319  | 120                          |  |  |
| Units: Participants         | 284  | 80                           |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Disease control rate (DCR)                                       |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 439  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 5.79   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 3.18   |
| upper limit                             | 10.55  |

## Secondary: Duration of Response (DOR)

|  |   |
|--|---|
| End point title  | Duration of Response (DOR) <sup>[5]</sup> |
| End point description:   |   |
| Duration of Response (DOR) was defined as the duration between the date of first documented Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) and the date of first documented radiographic progression or death due to any cause as per central review assessment. |   |
| End point type   | Secondary                                 |
| End point timeframe:   |   |
| From first documented evidence of CR or PR (the response prior to confirmation) until time of documented disease progression or death due to any cause, whichever comes first, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)  |   |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| <b>End point values</b>          | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 95   | 2                            |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 9.8 (9.1 to 11.7)                              | 10.6 (0 to 999)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first Symptomatic Skeletal Event (SSE)

|                 |   |
|-----------------|---|
| End point title | Time to first Symptomatic Skeletal Event (SSE) <sup>[6]</sup> |
|-----------------|---|

End point description:

Time to first Symptomatic Skeletal Event (SSE) was defined as the time (in months) from the date of randomization to the date of the SSE or death from any cause. The SSE date was the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death due to any cause, whichever occurred first. SSE data for this endpoint were collected up through EOT visit. The censoring date was date of the last study visit (on or before the EOT visit).

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

End point timeframe:

From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                 | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 385  | 196                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 11.5 (10.3 to 13.2)                            | 6.8 (5.2 to 8.5)             |  |  |

## Statistical analyses

| Statistical analysis title              | Time to first Symptomatic Skeletal Event (SSE)                   |
|---|--|
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 581  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.5  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.4     |
| upper limit         | 0.62    |

## Secondary: Best percentage change from baseline in prostate-specific antigen (PSA) level

|                 |  |
|-----------------|--|
| End point title | Best percentage change from baseline in prostate-specific antigen (PSA) level <sup>[7]</sup> |
|-----------------|--|

End point description:

Best percentage change from baseline in PSA level was defined as the maximum percent decrease at any time post-baseline, including only patients with a baseline value and at least one non-missing post-baseline value (scheduled and unscheduled).

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

|                                      |  |                              |  |  |
|--------------------------------------|--|------------------------------|--|--|
| <b>End point values</b>              | Main Study:<br>177Lu-PSMA-617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type                   | Reporting group                            | Reporting group              |  |  |
| Number of subjects analysed          | 333  | 138                          |  |  |
| Units: Percentage change             |  |                              |  |  |
| arithmetic mean (standard deviation) | -20.9 (± 142.6)                            | 50.4 (± 118.4)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free survival (PFS)

|                 |  |
|-----------------|--|
| End point title | Progression-free survival (PFS) <sup>[8]</sup> |
|-----------------|--|

End point description:

Progression-free survival (PFS) was defined as the time (in months) from the date of randomization to the date of first evidence of radiographic, clinical or PSA progression or death due to any cause, whichever occurred first.

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

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever come first, assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study



|                                  |  |                              |  |  |
|----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>          | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 385  | 196                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 5.9 (5.2 to 6.6)                               | 2.4 (2.2 to 3.0)             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Progression-free survival (PFS)                                  |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 581  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Logrank  |
| Parameter estimate                      | Cox proportional hazard  |
| Point estimate                          | 0.3  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.24   |
| upper limit                             | 0.38   |

## Secondary: Percentage of participants achieving prostate-specific antigen (PSA) response

|                 |  |
|-----------------|--|
| End point title | Percentage of participants achieving prostate-specific antigen (PSA) response <sup>[9]</sup> |
|-----------------|--|

End point description:

PSA response was defined as the proportion of patients who had a  $\geq 50\%$  decrease in PSA from baseline confirmed by a PSA measurement  $\geq 4$  weeks later.

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

|                                   |  |                              |  |  |
|-----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>           | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type                | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed       | 385  | 196                          |  |  |
| Units: Percentage of participants |  |                              |  |  |

|                                  |                     |                   |  |  |
|----------------------------------|---------------------|-------------------|--|--|
| number (confidence interval 95%) | 46.0 (40.9 to 51.1) | 7.1 (4.0 to 11.7) |  |  |
|----------------------------------|---------------------|-------------------|--|--|

## Statistical analyses

| Statistical analysis title              | % of participants achieving PSA response                         |
|---|--|
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 581  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 11.19  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 6.3  |
| upper limit                             | 20   |

## Secondary: Duration of PSA response

|                 |  |
|-----------------|--|
| End point title | Duration of PSA response <sup>[10]</sup> |
|-----------------|--|

### End point description:

Duration of PSA response was defined as the duration between the date of first document PSA response (i.e.  $\geq 50\%$  decrease in PSA from Baseline) and the earliest date of PSA progression, where date of PSA progression was defined as: 1) Where a decline from baseline was documented, date that a  $\geq 25\%$  increase in PSA and an absolute increase of 2 ng/mL or more from the nadir was documented and confirmed by a second consecutive value obtained at least 3 weeks later. Rises in PSA within the first 12 weeks of the date of first dose of randomized treatment were ignored; 2) Where no decline from baseline was documented, PSA progression was defined as a  $\geq 25\%$  increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks from the date of first dose of randomized treatment (without confirmation) as specified in the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) guidelines.

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

### End point timeframe:

From date of first documented PSA response till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

### Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

|                                  |  |                              |  |  |
|----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>          | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 177  | 14                           |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 8.9 (7.6 to<br>10.7)                           | 4.4 (2.6 to<br>10.8)         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Prostate-specific antigen 80 (PSA80) response

|                 |   |
|-----------------|---|
| End point title | Prostate-specific antigen 80 (PSA80) response <sup>[11]</sup> |
|-----------------|---|

End point description:

PSA80 response was defined as the proportion of participants who had a  $\geq 80\%$  decrease in PSA from baseline confirmed by a PSA measurement  $\geq 4$  weeks later.

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

|                                   |  |                              |  |  |
|-----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>           | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type                | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed       | 385  | 196                          |  |  |
| Units: Percentage of participants |  |                              |  |  |
| number (confidence interval 95%)  | 33.0 (28.3 to<br>37.9)                         | 2.0 (0.6 to 5.1)             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Prostate-specific antigen 80 (PSA80) response                    |
| Comparison groups                       | Main Study: 177Lu-PSMA-617 + BS/BSOC v Main Study: BS/BSOC alone |
| Number of subjects included in analysis | 581  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 23.6   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 8.6     |
| upper limit         | 65.1    |

### Secondary: Best percentage change from baseline in alkaline phosphatase (ALP) level

|                 |  |
|-----------------|--|
| End point title | Best percentage change from baseline in alkaline phosphatase (ALP) level <sup>[12]</sup> |
|-----------------|--|

End point description:

Best percentage change from baseline in alkaline phosphatase (ALP) level was defined as the maximum percent decrease at any time post-baseline, including only patients with a baseline value and at least one non-missing post-baseline value (scheduled and unscheduled).

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                     | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--------------------------------------|--|------------------------------|--|--|
| Subject group type                   | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed          | 372  | 172                          |  |  |
| Units: Percentage change             |  |                              |  |  |
| arithmetic mean (standard deviation) | -14.4 (± 46.3)                                 | 0.6 (± 33.8)                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to worsening in BPI-SF pain intensity scale

|                 |  |
|-----------------|--|
| End point title | Time to worsening in BPI-SF pain intensity scale <sup>[13]</sup> |
|-----------------|--|

End point description:

Time to worsening in BPI-SF pain intensity scale was defined as the time from randomization to the first occurring of an increase of worsening threshold ( $\geq 30\%$  of baseline or  $\geq 2$ -point increase) at any time up through EOT visit compared to baseline, clinical disease progression, or death.

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

End point timeframe:

From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                 | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 328  | 166                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 5.9 (4.8 to 6.9)                               | 2.2 (1.8 to 2.8)             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best percentage change from baseline in lactate dehydrogenase (LDH) level

|                 |   |
|-----------------|---|
| End point title | Best percentage change from baseline in lactate dehydrogenase (LDH) level <sup>[14]</sup> |
|-----------------|---|

End point description:

Best percentage change from baseline in lactate dehydrogenase (LDH) level was defined as the maximum percent decrease at any time post-baseline, including only patients with a baseline value and at least one non-missing post-baseline value (scheduled and unscheduled).

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                     | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--------------------------------------|--|------------------------------|--|--|
| Subject group type                   | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed          | 371  | 168                          |  |  |
| Units: Percentage change             |  |                              |  |  |
| arithmetic mean (standard deviation) | -23.1 (± 23.8)                                 | -9.2 (± 28.2)                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to improvement after worsening in BPI-SF pain intensity scale

|   |  |
|---|--|
| End point title   | Time to improvement after worsening in BPI-SF pain intensity scale <sup>[15]</sup> |
| End point description:<br>Time to improvement after worsening in BPI-SF pain intensity scale was defined as the time from worsening of Pain Intensity score to a Pain Intensity score ≤ baseline.   |  |
| End point type  | Secondary  |
| End point timeframe:<br>From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)   |  |
| Notes:<br>[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: Only applicable to study arms for the Main Study |  |

|                                  |  |                              |  |  |
|----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>          | Main Study:<br>177Lu-PSMA-617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type               | Reporting group                            | Reporting group              |  |  |
| Number of subjects analysed      | 144  | 76                           |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 2.8 (1.9 to 4.2)                           | 4.2 (2.8 to 11.3)            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to worsening in BPI-SF pain interference scale

|   |   |
|---|---|
| End point title   | Time to worsening in BPI-SF pain interference scale <sup>[16]</sup> |
| End point description:<br>Time to worsening in BPI-SF pain interference scale was defined as the time from randomization to the first occurring of 1) an increase of worsening threshold (≥30% of baseline or ≥2-point increase) at any time up through EOT visit compared to baseline, 2) clinical disease progression, or 3) death. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)   |   |
| Notes:<br>[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: Only applicable to study arms for the Main Study                                 |   |

|                                  |  |                              |  |  |
|----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>          | Main Study:<br>177Lu-PSMA-617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type               | Reporting group                            | Reporting group              |  |  |
| Number of subjects analysed      | 330  | 166                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 5.0 (4.2 to 6.1)                           | 2.3 (1.7 to 2.9)             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to improvement after worsening in BPI-SF pain interference scale

|                 |   |
|-----------------|---|
| End point title | Time to improvement after worsening in BPI-SF pain interference scale <sup>[17]</sup> |
|-----------------|---|

End point description:

Time to improvement after worsening in BPI-SF pain interference scale was defined as the time from worsening of Pain Interference score to a Pain Interference score  $\leq$  baseline.

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

End point timeframe:

From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

|                                  |  |                              |  |  |
|----------------------------------|--|------------------------------|--|--|
| <b>End point values</b>          | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 176  | 72                           |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 3.0 (2.8 to 4.4)                               | 2.8 (1.7 to 999)             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to worsening in BPI-SF worst pain intensity scale (time to disease related pain)

|                 |   |
|-----------------|---|
| End point title | Time to worsening in BPI-SF worst pain intensity scale (time to disease related pain) <sup>[18]</sup> |
|-----------------|---|

End point description:

Time to worsening in BPI-SF worst pain intensity scale (time to disease related pain) was defined as the time from randomization to the first occurring of worsening exceeding the threshold threshold ( $\geq 30\%$  of baseline or  $\geq 2$  point increase) at any time up through EOT visit compared to baseline, clinical disease progression, or death.

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

End point timeframe:

From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                 | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 332  | 169                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 5.0 (4.2 to 5.9)                               | 2.0 (1.7 to 2.2)             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in BPI-SF (Brief-Pain Inventory - Short Form) pain intensity scale

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in BPI-SF (Brief-Pain Inventory - Short Form) pain intensity scale <sup>[19]</sup> |
|-----------------|---|

End point description:

The BPI-SF is a generic pain assessment tool used in research and practice for pain assessment in musculoskeletal conditions. The higher the BPI-SF score, the worse the pain. The BPI-SF consists of 4 questions regarding pain intensity (worst pain intensity, least pain intensity, average pain intensity and pain right now), 2 questions on the use of analgesics, and 7 questions on how the level pain has interfered with the subject's life (General Activity, Mood, Walking Ability, Normal Work, Relations with other people, Sleep, Enjoyment of Life). Intensity items consist of an 11-response rating scale scored from 0 ("No Pain") to 10 ("Pain As Bad As You Can Imagine"). BPI-SF Pain intensity is the mean of non-missing items of the 4 individual scales, if there are 3 or more items not missing; otherwise this scale is set to missing.

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

End point timeframe:

Baseline (BL), Cycle 2 to Cycle 13 (Week 1 Day 1), End of Treatment (EoT) (cycle duration for Cycle 1-6 = 6 weeks and for Cycle 7 and beyond = 12 weeks)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                      | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|---------------------------------------|--|------------------------------|--|--|
| Subject group type                    | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed           | 385  | 196                          |  |  |
| Units: Score on a scale               |  |                              |  |  |
| arithmetic mean (standard deviation)  |  |                              |  |  |
| Cycle 2, Week 1, Day 1 change from BL | -0.59 (± 2.037)                                | 0.21 (± 2.404)               |  |  |
| Cycle 3, Week 1, Day 1 change from BL | -0.62 (± 1.924)                                | 0.02 (± 2.033)               |  |  |



|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| Cycle 4, Week 1, Day 1 change from BL  | -0.42 (± 2.017) | 0.26 (± 2.383)  |  |  |
| Cycle 5, Week 1, Day 1 change from BL  | -0.49 (± 1.957) | 0.55 (± 3.144)  |  |  |
| Cycle 6, Week 1, Day 1 change from BL  | -0.41 (± 1.897) | 0.10 (± 2.740)  |  |  |
| Cycle 7, Week 1, Day 1 change from BL  | -0.48 (± 2.011) | -0.32 (± 1.585) |  |  |
| Cycle 8, Week 1, Day 1 change from BL  | -0.18 (± 1.759) | -1.10 (± 2.205) |  |  |
| Cycle 9, Week 1, Day 1 change from BL  | -0.70 (± 2.157) | 0.13 (± 1.780)  |  |  |
| Cycle 10, Week 1, Day 1 change from BL | 0.02 (± 1.513)  | 0.50 (± 1.768)  |  |  |
| Cycle 11, Week 1, Day 1 change from BL | -0.40 (± 0.956) | 0.75 (± 1.768)  |  |  |
| Cycle 12, Week 1, Day 1 change from BL | -1.00 (± 0.354) | 999 (± 999)     |  |  |
| Cycle 13, Week 1, Day 1 change from BL | -0.75 (± 999)   | 999 (± 999)     |  |  |
| End of Treatment (EoT) change from BL  | 0.46 (± 2.415)  | 0.50 (± 2.405)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in BPI-SF (Brief-Pain Inventory - Short Form) pain interference scale

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in BPI-SF (Brief-Pain Inventory - Short Form) pain interference scale <sup>[20]</sup> |
|-----------------|--|

End point description:

The BPI-SF is a generic pain assessment tool used in research and practice for pain assessment in musculoskeletal conditions. The higher the BPI-SF score, the worse the pain. The BPI-SF consists of 4 questions regarding pain intensity (worst pain intensity, least pain intensity, average pain intensity and pain right now), 2 questions on the use of analgesics, and 7 questions on how the level pain has interfered with the subject's life (General Activity, Mood, Walking Ability, Normal Work, Relations with other people, Sleep, Enjoyment of Life). Interference items consist of scores from 0 ("Does Not Interfere") to 10 ("Completely Interferes"). BPI-SF Interference scale is the mean of non-missing items of the 7 items on pain interference, if there are 4 or more items not missing; otherwise this scale is set to missing.

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

End point timeframe:

Baseline (BL), Cycle 2 to Cycle 13 (Week 1 Day 1), End of Treatment (EoT) (cycle duration for Cycle 1-6 = 6 weeks and for Cycle 7 and beyond = 12 weeks)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                       | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--|--|------------------------------|--|--|
| Subject group type                     | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed            | 385  | 196                          |  |  |
| Units: Score on a scale                |  |                              |  |  |
| arithmetic mean (standard deviation)   |  |                              |  |  |
| Cycle 2, Week 1, Day 1 change from BL  | -0.40 (± 2.167)                                | 0.58 (± 2.700)               |  |  |
| Cycle 3, Week 1, Day 1 change from BL  | -0.35 (± 2.348)                                | -0.15 (± 2.216)              |  |  |
| Cycle 4, Week 1, Day 1 change from BL  | -0.33 (± 2.249)                                | 0.21 (± 2.762)               |  |  |
| Cycle 5, Week 1, Day 1 change from BL  | -0.32 (± 2.223)                                | 0.52 (± 3.480)               |  |  |
| Cycle 6, Week 1, Day 1 change from BL  | -0.28 (± 2.166)                                | 0.49 (± 3.354)               |  |  |
| Cycle 7, Week 1, Day 1 change from BL  | -0.22 (± 1.882)                                | 0.06 (± 2.570)               |  |  |
| Cycle 8, Week 1, Day 1 change from BL  | 0.18 (± 1.926)                                 | -0.26 (± 1.291)              |  |  |
| Cycle 9, Week 1, Day 1 change from BL  | -0.15 (± 1.751)                                | 0.12 (± 1.667)               |  |  |
| Cycle 10, Week 1, Day 1 change from BL | 0.62 (± 2.141)                                 | 1.50 (± 1.313)               |  |  |
| Cycle 11, Week 1, Day 1 change from BL | -0.06 (± 1.334)                                | 0.36 (± 4.748)               |  |  |
| Cycle 12, Week 1, Day 1 change from BL | -0.89 (± 0.914)                                | 999 (± 999)                  |  |  |
| Cycle 13, Week 1, Day 1 change from BL | -0.43 (± 999)                                  | 999 (± 999)                  |  |  |
| End of Treatment (EoT) change from BL  | 0.73 (± 2.756)                                 | 0.29 (± 2.385)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to worsening in FACT-P total score

|                 |   |
|-----------------|---|
| End point title | Time to worsening in FACT-P total score <sup>[21]</sup> |
|-----------------|---|

End point description:

Time to worsening was defined as the time from randomization to the first occurring of a  $\geq 10$  point decrease in FACT-P total score compared to baseline, clinical disease progression, or death.

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

End point timeframe:

From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                 | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed      | 385  | 196                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 5.7 (4.8 to 6.6)                               | 2.2 (1.8 to 2.8)             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in FACT-P (Functional Assessment of Cancer Therapy – Prostate) Total Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in FACT-P (Functional Assessment of Cancer Therapy – Prostate) Total Score <sup>[22]</sup> |
|-----------------|---|

End point description:

The FACT-P total score (range 0-156) consist of five subscales (Physical (0-28), Functional (0-28), Social (0-28), and Emotional Well-being (0-24)) and a functional well-being and prostate cancer subscale (range 0-48). Higher scores indicate higher degree of functioning and better quality of life.

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

End point timeframe:

Baseline (BL), Cycle 2 to Cycle 13 (Week 1 Day 1), End of Treatment (EoT) (cycle duration for Cycle 1-6 = 6 weeks and for Cycle 7 and beyond = 12 weeks)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                       | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--|--|------------------------------|--|--|
| Subject group type                     | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed            | 385  | 196                          |  |  |
| Units: Score on a scale                |  |                              |  |  |
| arithmetic mean (standard deviation)   |  |                              |  |  |
| Cycle 2, Week 1, Day 1 change from BL  | 3.6 (± 16.63)                                  | -7.2 (± 17.85)               |  |  |
| Cycle 3, Week 1, Day 1 change from BL  | 3.8 (± 17.48)                                  | -2.6 (± 14.00)               |  |  |
| Cycle 4, Week 1, Day 1 change from BL  | 5.4 (± 15.93)                                  | -1.3 (± 18.40)               |  |  |
| Cycle 5, Week 1, Day 1 change from BL  | 4.0 (± 16.24)                                  | -5.9 (± 27.83)               |  |  |
| Cycle 6, Week 1, Day 1 change from BL  | 4.1 (± 15.22)                                  | -5.0 (± 26.87)               |  |  |
| Cycle 7, Week 1, Day 1 change from BL  | 4.9 (± 16.47)                                  | -2.9 (± 17.89)               |  |  |
| Cycle 8, Week 1, Day 1 change from BL  | 3.8 (± 15.87)                                  | -13.0 (± 32.76)              |  |  |
| Cycle 9, Week 1, Day 1 change from BL  | 3.8 (± 14.22)                                  | 6.9 (± 5.92)                 |  |  |
| Cycle 10, Week 1, Day 1 change from BL | 0.0 (± 18.27)                                  | 0.2 (± 14.14)                |  |  |
| Cycle 11, Week 1, Day 1 change from BL | -0.8 (± 20.99)                                 | 8.2 (± 33.71)                |  |  |
| Cycle 12, Week 1, Day 1 change from BL | 10.3 (± 12.11)                                 | 999 (± 999)                  |  |  |

|  |                |                 |  |  |
|--|----------------|-----------------|--|--|
| Cycle 13, Week 1, Day 1 change from BL | 30.0 (± 999)   | 999 (± 999)     |  |  |
| End of Treatment (EoT) change from BL  | -9.4 (± 21.64) | -10.4 (± 18.59) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to worsening in EQ-5D-5L utility score

|                 |   |
|-----------------|---|
| End point title | Time to worsening in EQ-5D-5L utility score <sup>[23]</sup> |
|-----------------|---|

End point description:

Time to worsening for utility score was defined as time from randomization to the first occurrence of worsening in utility score relative to baseline (no change or any decrease), clinical disease progression, or death.

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

End point timeframe:

From date of randomization until date of End of Treatment (EoT), assessed up to 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                 | Main Study:<br>177Lu-PSMA-617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|----------------------------------|--|------------------------------|--|--|
| Subject group type               | Reporting group                            | Reporting group              |  |  |
| Number of subjects analysed      | 385  | 196                          |  |  |
| Units: Months                    |  |                              |  |  |
| median (confidence interval 95%) | 1.0 (0.7 to 1.8)                           | 0.5 (0.4 to 1.0)             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the European Quality of Life (EuroQol) – 5 Domain 5 Level scale (EQ-5D-5L) utility score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the European Quality of Life (EuroQol) – 5 Domain 5 Level scale (EQ-5D-5L) utility score <sup>[24]</sup> |
|-----------------|--|

End point description:

The EQ-5D-5L is a standardized participant completed questionnaire that measures health-related quality of life. EQ-5D-5L consists of two components: a health state profile and an optional visual analogue scale (VAS). EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2= slight problems, 3=moderate problems, 4= severe problems, and 5= extreme problems. Higher scores indicated greater levels of problems across each of the five dimensions. A utility score was obtained by using a weighted combination of the levels of the five dimension-scales. The weights were based on value sets which were country-specific for the U.K. Utility scores ranges from the lowest possible score for a living patient of -0.594 (when all responses are '5') to 1 (when all responses are '1'). If a patient died, he was assigned a score of 0 on the date of death.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline (BL), Cycle 2 to Cycle 13 (Week 1 Day 1), End of Treatment (EoT) (cycle duration for Cycle 1-6 = 6 weeks and for Cycle 7 and beyond = 12 weeks)   |           |
| Notes:   |           |
| [24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. |           |
| Justification: Only applicable to study arms for the Main Study  |           |

| End point values                       | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--|--|------------------------------|--|--|
| Subject group type                     | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed            | 385  | 196                          |  |  |
| Units: Score on a scale                |  |                              |  |  |
| arithmetic mean (standard deviation)   |  |                              |  |  |
| Cycle 2, Week 1, Day 1 change from BL  | 0.0221 (± 0.17693)                             | -0.0897 (± 0.24973)          |  |  |
| Cycle 3, Week 1, Day 1 change from BL  | 0.0297 (± 0.18817)                             | -0.0331 (± 0.14155)          |  |  |
| Cycle 4, Week 1, Day 1 change from BL  | 0.0292 (± 0.17713)                             | -0.0818 (± 0.23752)          |  |  |
| Cycle 5, Week 1, Day 1 change from BL  | 0.0398 (± 0.16827)                             | -0.0673 (± 0.28633)          |  |  |
| Cycle 6, Week 1, Day 1 change from BL  | 0.0342 (± 0.17950)                             | -0.0110 (± 0.17842)          |  |  |
| Cycle 7, Week 1, Day 1 change from BL  | 0.0252 (± 0.16127)                             | -0.0088 (± 0.09081)          |  |  |
| Cycle 8, Week 1, Day 1 change from BL  | 0.0285 (± 0.18017)                             | -0.0296 (± 0.14964)          |  |  |
| Cycle 9, Week 1, Day 1 change from BL  | 0.0100 (± 0.17447)                             | 0.0087 (± 0.08167)           |  |  |
| Cycle 10, Week 1, Day 1 change from BL | 0.0134 (± 0.15764)                             | -0.0655 (± 0.09263)          |  |  |
| Cycle 11, Week 1, Day 1 change from BL | 0.0464 (± 0.16858)                             | 0.0250 (± 0.19940)           |  |  |
| Cycle 12, Week 1, Day 1 change from BL | 0.1118 (± 0.13833)                             | 999 (± 999)                  |  |  |
| Cycle 13, Week 1, Day 1 change from BL | 0.0640 (± 999)                                 | 999 (± 999)                  |  |  |
| End of Treatment (EoT) change from BL  | -0.0939 (± 0.22698)                            | -0.0900 (± 0.21223)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the European Quality of Life (EuroQoL) – 5 Domain 5 Level scale (EQ-5D-5L) EQ-VAS

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the European Quality of Life (EuroQoL) – 5 Domain 5 Level scale (EQ-5D-5L) EQ-VAS <sup>[25]</sup> |
|-----------------|---|

End point description:

The EQ-5D-5L is a standardized participant completed questionnaire that measures health-related quality of life. EQ-5D-5L consists of two components: a health state profile and an optional visual

analogue scale (VAS). EQ VAS records the patient's self-rated health on a vertical visual analogue 0-100 scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The higher the EQ-VAS score, the better the QoL.

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

End point timeframe:

Baseline (BL), Cycle 2 to Cycle 13 (Week 1 Day 1), End of Treatment (EoT) (cycle duration for Cycle 1-6 = 6 weeks and for Cycle 7 and beyond = 12 weeks)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                       | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--|--|------------------------------|--|--|
| Subject group type                     | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed            | 385  | 196                          |  |  |
| Units: Score on a scale                |  |                              |  |  |
| arithmetic mean (standard deviation)   |  |                              |  |  |
| Cycle 2, Week 1, Day 1 change from BL  | 1.8 (± 19.98)                                  | -7.2 (± 20.31)               |  |  |
| Cycle 3, Week 1, Day 1 change from BL  | 1.4 (± 19.82)                                  | -3.8 (± 21.50)               |  |  |
| Cycle 4, Week 1, Day 1 change from BL  | 2.8 (± 19.18)                                  | -1.7 (± 18.73)               |  |  |
| Cycle 5, Week 1, Day 1 change from BL  | 4.0 (± 17.30)                                  | -8.5 (± 28.88)               |  |  |
| Cycle 6, Week 1, Day 1 change from BL  | 2.1 (± 19.61)                                  | 3.2 (± 19.43)                |  |  |
| Cycle 7, Week 1, Day 1 change from BL  | 3.6 (± 20.64)                                  | 5.9 (± 12.79)                |  |  |
| Cycle 8, Week 1, Day 1 change from BL  | 0.6 (± 17.18)                                  | 13.8 (± 16.60)               |  |  |
| Cycle 9, Week 1, Day 1 change from BL  | 0.1 (± 19.68)                                  | 6.3 (± 20.82)                |  |  |
| Cycle 10, Week 1, Day 1 change from BL | 2.9 (± 13.97)                                  | -8.0 (± 2.83)                |  |  |
| Cycle 11, Week 1, Day 1 change from BL | 5.8 (± 10.33)                                  | -9.0 (± 28.28)               |  |  |
| Cycle 12, Week 1, Day 1 change from BL | 4.5 (± 13.03)                                  | 999 (± 999)                  |  |  |
| Cycle 13, Week 1, Day 1 change from BL | -5.0 (± 999)                                   | 999 (± 999)                  |  |  |
| End of Treatment (EoT) change from BL  | -8.9 (± 22.07)                                 | -10.1 (± 21.49)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants hospitalized as in-patient

|                 |   |
|-----------------|---|
| End point title | Number of participants hospitalized as in-patient <sup>[26]</sup> |
|-----------------|---|

End point description:

The number of hospitalizations (yes/no) (admitted as in-patient) was collected as part of the hospital admission for health economic evaluations.

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values            | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|-----------------------------|--|------------------------------|--|--|
| Subject group type          | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed | 385  | 196                          |  |  |
| Units: Participants         |  |                              |  |  |
| Yes                         | 157  | 59                           |  |  |
| No                          | 228  | 137                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of time in hospital following 177Lu-PSMA-617 administration

|   |  |
|---|--|
| End point title   | Duration of time in hospital following 177Lu-PSMA-617 administration <sup>[27]</sup> |
| End point description:<br>The duration of time in hospital following 177Lu-PSMA-617 administration (hours) was the time span of patient discharged as captured on the 177Lu-PSMA-617 administration Case Report Form (CRF). |  |
| End point type  | Secondary  |

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                     | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|--------------------------------------|--|------------------------------|--|--|
| Subject group type                   | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed          | 341  | 0 <sup>[28]</sup>            |  |  |
| Units: Hours                         |  |                              |  |  |
| arithmetic mean (standard deviation) | 28.25 (±<br>46.578)                            | ( )                          |  |  |

Notes:

[28] - This endpoint only apply to the Main Study "177Lu-PSMA-617 + BS/BSOC" arm

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concomitant drug use for health economics analysis

|   |  |
|---|--|
| End point title   | Concomitant drug use for health economics analysis <sup>[29]</sup> |
| End point description:  |  |
| The list of concomitant drugs as captured on the concomitant medication/therapy CRF page to include in each category was pre-specified and flagged prior to the pre planned analyses. (1) Bisphosphonates (including but not limited to zoledronic acid, alendronic acid, etc.), denosumab, and other bone targeted therapies), (2) Corticosteroids for systemic use (3), Antifungals for systemic use (i.e. ketoconazole), (4) ESA (erythropoietin stimulating agents, i.e. epoetin alfa), (5) Granulocyte macrophage colony-stimulating factor (GM-CSF), (6) Novel androgen axis drugs (NAADs; i.e. enzalutamide, abiraterone, apalutamide), (7) Antiemetics and (8) Opioid analgesics use for cancer-related pain. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)  |  |
| Notes:  |  |
| [29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  |  |
| Justification: Only applicable to study arms for the Main Study   |  |

| End point values                      | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|---------------------------------------|--|------------------------------|--|--|
| Subject group type                    | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed           | 385  | 196                          |  |  |
| Units: Participants                   |  |                              |  |  |
| Bisphosphonates Yes                   | 169  | 88                           |  |  |
| Corticosteroids Yes                   | 246  | 113                          |  |  |
| Antifungals Yes                       | 1  | 4                            |  |  |
| Erythropoietin Stimulating Agents Yes | 8  | 2                            |  |  |
| GM-CSF Yes                            | 7  | 3                            |  |  |
| Novel Androgen Axis Drugs Yes         | 188  | 115                          |  |  |
| Antiemetics Yes                       | 232  | 45                           |  |  |
| Opioid analgesics Yes                 | 199  | 96                           |  |  |
| Bisphosphonates No                    | 216  | 108                          |  |  |
| Corticosteroids No                    | 139  | 83                           |  |  |
| Antifungals No                        | 384  | 192                          |  |  |
| Erythropoietin Stimulating Agents No  | 377  | 194                          |  |  |
| GM-CSF No                             | 378  | 193                          |  |  |
| Novel Androgen Axis Drugs No          | 197  | 81                           |  |  |
| Antiemetics No                        | 153  | 151                          |  |  |
| Opioid analgesics No                  | 186  | 100                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Therapeutic interventions for health economics analysis

|  |   |
|--|---|
| End point title  | Therapeutic interventions for health economics analysis <sup>[30]</sup> |
| End point description:   |   |
| The list of therapeutic interventions was pre-specified and flagged prior to the pre planned analyses as captured on: 1) the concurrent radiotherapy CRF page to include local external beam radiotherapy (inclusive of palliative external radiation), 2) on the concomitant medication/therapy CRF page to |   |



include blood transfusion (full blood or derivatives).

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

End point timeframe:

From date of randomization till 30 days safety fup, assessed up to approximately 32 months (Primary Analysis cut-off date = 27-Jan-2021)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only applicable to study arms for the Main Study

| End point values                | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone |  |  |
|---------------------------------|--|------------------------------|--|--|
| Subject group type              | Reporting group                                | Reporting group              |  |  |
| Number of subjects analysed     | 385  | 196                          |  |  |
| Units: Participants             |  |                              |  |  |
| Local external beam therapy Yes | 63   | 37                           |  |  |
| Blood transfusion Yes           | 74   | 13                           |  |  |
| Local external beam therapy No  | 322  | 159                          |  |  |
| Blood transfusion No            | 311  | 183                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: All collected deaths

|                 |                      |
|-----------------|----------------------|
| End point title | All collected deaths |
|-----------------|----------------------|

End point description:

Pre-treatment deaths were collected from day of participant's informed consent to the day before first dose of study medication.

On-treatment deaths were collected from first dose of study medication to 30 days after last dose of study medication (on-treatment), up to approximately 43 months.

Deaths were collected in the post treatment survival follow up from 31 days after last dose of study medication until the end of the study, up to approximately 66 months. These are not considered AEs

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Pre-treatment deaths: Up to 28 days prior to treatment. On-treatment deaths: Up to approximately 43 months. Post-treatment deaths: Up to approximately 66 months

| End point values            | Main Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC | Main Study:<br>BS/BSOC alone | Sub Study:<br>177Lu-PSMA-<br>617 +<br>BS/BSOC |  |
|-----------------------------|--|------------------------------|---|--|
| Subject group type          | Reporting group                                | Reporting group              | Reporting group                               |  |
| Number of subjects analysed | 551  | 280                          | 30  |  |
| Units: Participants         |  |                              |   |  |
| Pre-treatment deaths        | 0  | 0                            | 0   |  |
| On-treatment deaths         | 68   | 19                           | 5   |  |
| Post-treatment deaths       | 389  | 182                          | 16  |  |

|            |     |     |    |  |
|------------|-----|-----|----|--|
| All deaths | 457 | 201 | 21 |  |
|------------|-----|-----|----|--|

**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from first dose of study medication until the last dose plus 30 days post-treat follow-up, assessed up to approximately 43 months.

Adverse event reporting additional description:

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

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

### Reporting groups

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | -Main Study-@Lu-PSMA-617+@BSC/BSOC |
|-----------------------|------------------------------------|

Reporting group description:

-Main Study-@Lu-PSMA-617+@BSC/BSOC

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | -Sub Study-@Lu-PSMA-617+@BSC/BSOC |
|-----------------------|-----------------------------------|

Reporting group description:

-Sub Study-@Lu-PSMA-617+@BSC/BSOC

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | -Main Study-@BSC/BSOC@only |
|-----------------------|----------------------------|

Reporting group description:

-Main Study-@BSC/BSOC@only

| Serious adverse events  | -Main Study-@Lu-PSMA-617+@BSC/BSOC | -Sub Study-@Lu-PSMA-617+@BSC/BSOC | -Main Study-@BSC/BSOC@only |
|---|------------------------------------|-----------------------------------|----------------------------|
| Total subjects affected by serious adverse events                   |                                    |                                   |                            |
| subjects affected / exposed   | 195 / 529 (36.86%)                 | 9 / 30 (30.00%)                   | 58 / 205 (28.29%)          |
| number of deaths (all causes)                                       | 68                                 | 5                                 | 19                         |
| number of deaths resulting from adverse events                      | 5                                  | 0                                 | 0                          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                    |                                   |                            |
| Cancer pain   |                                    |                                   |                            |
| subjects affected / exposed   | 0 / 529 (0.00%)                    | 1 / 30 (3.33%)                    | 0 / 205 (0.00%)            |
| occurrences causally related to treatment / all                     | 0 / 0                              | 0 / 1                             | 0 / 0                      |
| deaths causally related to treatment / all                          | 0 / 0                              | 0 / 0                             | 0 / 0                      |
| Metastases to central nervous system                                |                                    |                                   |                            |
| subjects affected / exposed   | 2 / 529 (0.38%)                    | 0 / 30 (0.00%)                    | 0 / 205 (0.00%)            |
| occurrences causally related to treatment / all                     | 0 / 2                              | 0 / 0                             | 0 / 0                      |
| deaths causally related to treatment / all                          | 0 / 1                              | 0 / 0                             | 0 / 0                      |
| Metastases to meninges  |                                    |                                   |                            |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Pancreatic carcinoma                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vascular disorders                              |                 |                |                 |
| Aortic stenosis                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Orthostatic hypotension                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Deep vein thrombosis                            |                 |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Embolism  |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Hypotension                                     |                 |                |                 |
| subjects affected / exposed                     | 4 / 529 (0.76%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Arteriosclerosis                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Surgical and medical procedures                 |                 |                |                 |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| Euthanasia   |                 |                |                 |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0          | 0 / 0           |
| Neck dissection                                      |                 |                |                 |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Pain management                                      |                 |                |                 |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                 |                |                 |
| Asthenia   |                 |                |                 |
| subjects affected / exposed                          | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Multiple organ dysfunction syndrome                  |                 |                |                 |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0          | 0 / 0           |
| Fatigue  |                 |                |                 |
| subjects affected / exposed                          | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| General physical health deterioration                |                 |                |                 |
| subjects affected / exposed                          | 0 / 529 (0.00%) | 1 / 30 (3.33%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1          | 0 / 1           |
| Generalised oedema                                   |                 |                |                 |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Influenza like illness                          |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Malaise   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Disease progression                             |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 1           |
| Oedema  |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Oedema peripheral                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pain  |                 |                |                 |
| subjects affected / exposed                     | 5 / 529 (0.95%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pyrexia   |                 |                |                 |
| subjects affected / exposed                     | 8 / 529 (1.51%) | 1 / 30 (3.33%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Systemic inflammatory response syndrome         |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Reproductive system and breast disorders        |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Benign prostatic hyperplasia                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Penile pain                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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, thoracic and mediastinal disorders |                 |                |                 |
| Acute respiratory failure                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Chronic obstructive pulmonary disease           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Dyspnoea  |                 |                |                 |
| subjects affected / exposed                     | 5 / 529 (0.95%) | 1 / 30 (3.33%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Haemoptysis                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypoxia   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Pleural effusion                                |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 1 / 30 (3.33%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Pulmonary embolism                              |                 |                |                 |
| subjects affected / exposed                     | 6 / 529 (1.13%) | 1 / 30 (3.33%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pulmonary hypertension                          |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Epistaxis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Psychiatric disorders                           |                 |                |                 |
| Confusional state                               |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Delirium  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Mental status changes                           |                 |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Mixed anxiety and depressive disorder           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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                                  |                 |                |                 |
| Blood creatinine increased                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Injury, poisoning and procedural complications  |                 |                |                 |
| Acetabulum fracture                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Fall  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Femoral neck fracture                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Femur fracture                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hip fracture                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Muscle strain                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Overdose  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Spinal fracture                                 |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Subdural haematoma                              |                 |                |                 |
| subjects affected / exposed                     | 4 / 529 (0.76%) | 0 / 30 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 1           |
| Wound complication                              |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Congenital, familial and genetic disorders      |                 |                |                 |
| Vascular malformation                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 disorders                               |                 |                |                 |
| Cardiomyopathy                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Arrhythmia                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Atrial fibrillation                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Cardiac failure congestive<br>subjects affected / exposed   | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Cardio-respiratory arrest<br>subjects affected / exposed    | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 1           |
| Myocardial infarction<br>subjects affected / exposed        | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Supraventricular tachycardia<br>subjects affected / exposed | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Ventricular tachycardia<br>subjects affected / exposed      | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to<br>treatment / all          | 1 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Nervous system disorders                                    |                 |                |                 |
| Brain oedema<br>subjects affected / exposed                 | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Cauda equina syndrome<br>subjects affected / exposed        | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Cerebellar infarction<br>subjects affected / exposed        | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          | 0 / 0           |
| Cerebral haemorrhage  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 infarction                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cognitive disorder                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Diplegia  |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Loss of consciousness                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Dysarthria                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Encephalopathy                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Haemorrhage intracranial                        |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0           |
| Headache  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Hypoglossal nerve paralysis                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Ischaemic stroke                                |                 |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Dizziness                                       |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Metabolic encephalopathy                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Myelopathy                                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pachymeningitis                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Paraesthesia                                    |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Paraplegia                                      |                 |                |                 |

|   |                 |                |                  |
|---|-----------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 529 (0.00%) | 1 / 30 (3.33%) | 0 / 205 (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 motor neuropathy                     |                 |                |                  |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| Tremor  |                 |                |                  |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| Spinal cord compression                         |                 |                |                  |
| subjects affected / exposed                     | 6 / 529 (1.13%) | 0 / 30 (0.00%) | 11 / 205 (5.37%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 0          | 1 / 11           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| Spinal cord disorder                            |                 |                |                  |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| Syncope   |                 |                |                  |
| subjects affected / exposed                     | 4 / 529 (0.76%) | 0 / 30 (0.00%) | 0 / 205 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0            |
| Transient ischaemic attack                      |                 |                |                  |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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            |
| Radiculopathy                                   |                 |                |                  |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| subjects affected / exposed                     | 2 / 529 (0.38%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| <b>Blood and lymphatic system disorders</b>     |                  |                |                 |
| <b>Anaemia</b>                                  |                  |                |                 |
| subjects affected / exposed                     | 15 / 529 (2.84%) | 2 / 30 (6.67%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 11 / 15          | 1 / 2          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| <b>Bone marrow failure</b>                      |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0          | 0 / 0           |
| <b>Febrile neutropenia</b>                      |                  |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| <b>Leukopenia</b>                               |                  |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| <b>Neutropenia</b>                              |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| <b>Pancytopenia</b>                             |                  |                |                 |
| subjects affected / exposed                     | 6 / 529 (1.13%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 5 / 6            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 2 / 2            | 0 / 0          | 0 / 0           |
| <b>Thrombocytopenia</b>                         |                  |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%)  | 2 / 30 (6.67%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3            | 2 / 2          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| <b>Ear and labyrinth disorders</b>              |                  |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Vertigo   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Eye disorders                                   |                 |                |                 |
| Vision blurred                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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                      |                 |                |                 |
| Diarrhoea                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Abdominal pain                                  |                 |                |                 |
| subjects affected / exposed                     | 4 / 529 (0.76%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Abdominal pain lower                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Ascites   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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                     | 5 / 529 (0.95%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 2 / 5           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Crohn's disease                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 1 / 30 (3.33%) | 0 / 205 (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           |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Duodenal ulcer                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric haemorrhage                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrooesophageal reflux disease                |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Haematemesis                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Rectal haemorrhage                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Intestinal perforation                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Intestinal pseudo-obstruction                   |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Large intestinal obstruction                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Lower gastrointestinal haemorrhage              |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nausea  |                 |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intestinal obstruction                          |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Small intestinal obstruction                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Stomatitis                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 gastrointestinal haemorrhage              |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Volvulus  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vomiting  |                 |                |                 |
| subjects affected / exposed                     | 5 / 529 (0.95%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 2 / 7           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                 |                |                 |
| Acute hepatic failure                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Cholecystitis                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Cholestasis                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Hepatic cytolysis                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatic failure                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Hepatic lesion                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Bile duct stenosis                              |                 |                |                 |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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 and urinary disorders                     |                  |                |                 |
| Acute kidney injury                             |                  |                |                 |
| subjects affected / exposed                     | 10 / 529 (1.89%) | 0 / 30 (0.00%) | 6 / 205 (2.93%) |
| occurrences causally related to treatment / all | 2 / 11           | 0 / 0          | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Dysuria   |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Urinary tract obstruction                       |                  |                |                 |
| subjects affected / exposed                     | 4 / 529 (0.76%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Haematuria                                      |                  |                |                 |
| subjects affected / exposed                     | 11 / 529 (2.08%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 2 / 12           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Hydronephrosis                                  |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Malignant urinary tract obstruction             |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Nephrolithiasis                                 |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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 tubular acidosis                          |                  |                |                 |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Urinary retention                               |                  |                |                 |
| subjects affected / exposed                     | 5 / 529 (0.95%)  | 1 / 30 (3.33%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| End stage renal disease                         |                  |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%)  | 1 / 30 (3.33%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1          | 0 / 0           |
| Endocrine disorders                             |                  |                |                 |
| Adrenal insufficiency                           |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Inappropriate antidiuretic hormone secretion    |                  |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%)  | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                  |                |                 |
| Flank pain                                      |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Arthralgia                                      |                  |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%)  | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Back pain                                       |                  |                |                 |
| subjects affected / exposed                     | 10 / 529 (1.89%) | 1 / 30 (3.33%) | 3 / 205 (1.46%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Bone pain                                       |                 |                |                 |
| subjects affected / exposed                     | 6 / 529 (1.13%) | 1 / 30 (3.33%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intervertebral disc compression                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Neck pain                                       |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Osteolysis                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Pathological fracture                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 stenosis                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 1 / 30 (3.33%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Spinal pain                                     |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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                     |                 |                |                 |
| Bacterial sepsis                                |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Appendicitis                                    |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Bronchitis                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| COVID-19  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Diverticulitis                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Enterococcal bacteraemia                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Enterocolitis infectious                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Escherichia sepsis                              |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Lower respiratory tract infection               |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Fungaemia                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Herpes zoster                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infection                                       |                 |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%) | 0 / 30 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Kidney infection                                |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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 sepsis                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Extradural abscess                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Osteomyelitis                                   |                 |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Pharyngitis                                     |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                 |                |                 |
| subjects affected / exposed                     | 7 / 529 (1.32%) | 0 / 30 (0.00%) | 3 / 205 (1.46%) |
| occurrences causally related to treatment / all | 2 / 7           | 0 / 0          | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Pneumonia aspiration                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| Pyelonephritis                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Pyelonephritis acute                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Wound infection                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Septic shock                                    |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Staphylococcal bacteraemia                      |                 |                |                 |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Streptococcal bacteraemia                       |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Urinary tract infection                         |                  |                |                 |
| subjects affected / exposed                     | 13 / 529 (2.46%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 15           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Urosepsis                                       |                  |                |                 |
| subjects affected / exposed                     | 3 / 529 (0.57%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Viral infection                                 |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Sepsis  |                  |                |                 |
| subjects affected / exposed                     | 10 / 529 (1.89%) | 0 / 30 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 1 / 10           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                  |                |                 |
| Cachexia  |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Decreased appetite                              |                  |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%)  | 0 / 30 (0.00%) | 0 / 205 (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           |
| Dehydration                                     |                  |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 5 / 529 (0.95%) | 1 / 30 (3.33%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Failure to thrive                               |                 |                |                 |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 0 / 205 (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           |
| Hypervolaemia                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypocalcaemia                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypoglycaemia                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hyponatraemia                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypophosphataemia                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Tumour lysis syndrome                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 0 / 30 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypokalaemia                                    |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 30 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | -Main Study-@Lu-PSMA-617+@BSC/BSOC | -Sub Study-@Lu-PSMA-617+@BSC/BSOC | -Main Study-@BSC/BSOC@only |
|---|------------------------------------|-----------------------------------|----------------------------|
| Total subjects affected by non-serious adverse events |                                    |                                   |                            |
| subjects affected / exposed                           | 502 / 529 (94.90%)                 | 28 / 30 (93.33%)                  | 151 / 205 (73.66%)         |
| Vascular disorders                                    |                                    |                                   |                            |
| Hypertension  |                                    |                                   |                            |
| subjects affected / exposed                           | 30 / 529 (5.67%)                   | 0 / 30 (0.00%)                    | 12 / 205 (5.85%)           |
| occurrences (all)                                     | 36                                 | 0                                 | 12                         |
| General disorders and administration site conditions  |                                    |                                   |                            |
| Extravasation   |                                    |                                   |                            |
| subjects affected / exposed                           | 0 / 529 (0.00%)                    | 2 / 30 (6.67%)                    | 0 / 205 (0.00%)            |
| occurrences (all)                                     | 0                                  | 2                                 | 0                          |
| Fatigue   |                                    |                                   |                            |
| subjects affected / exposed                           | 228 / 529 (43.10%)                 | 5 / 30 (16.67%)                   | 47 / 205 (22.93%)          |
| occurrences (all)                                     | 264                                | 5                                 | 49                         |
| General physical health deterioration                 |                                    |                                   |                            |
| subjects affected / exposed                           | 2 / 529 (0.38%)                    | 2 / 30 (6.67%)                    | 2 / 205 (0.98%)            |
| occurrences (all)                                     | 2                                  | 2                                 | 3                          |
| Oedema peripheral                                     |                                    |                                   |                            |
| subjects affected / exposed                           | 51 / 529 (9.64%)                   | 3 / 30 (10.00%)                   | 13 / 205 (6.34%)           |
| occurrences (all)                                     | 53                                 | 3                                 | 15                         |
| Pain  |                                    |                                   |                            |
| subjects affected / exposed                           | 28 / 529 (5.29%)                   | 2 / 30 (6.67%)                    | 10 / 205 (4.88%)           |
| occurrences (all)                                     | 30                                 | 2                                 | 11                         |
| Pyrexia   |                                    |                                   |                            |
| subjects affected / exposed                           | 30 / 529 (5.67%)                   | 1 / 30 (3.33%)                    | 7 / 205 (3.41%)            |
| occurrences (all)                                     | 35                                 | 1                                 | 7                          |
| Asthenia  |                                    |                                   |                            |

|  |                        |                     |                        |
|--|------------------------|---------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 34 / 529 (6.43%)<br>48 | 1 / 30 (3.33%)<br>1 | 16 / 205 (7.80%)<br>19 |
| Respiratory, thoracic and mediastinal disorders  |                        |                     |                        |
| Pleural effusion                                 |                        |                     |                        |
| subjects affected / exposed                      | 8 / 529 (1.51%)        | 2 / 30 (6.67%)      | 1 / 205 (0.49%)        |
| occurrences (all)                                | 8                      | 2                   | 1                      |
| Dyspnoea   |                        |                     |                        |
| subjects affected / exposed                      | 51 / 529 (9.64%)       | 2 / 30 (6.67%)      | 19 / 205 (9.27%)       |
| occurrences (all)                                | 58                     | 2                   | 19                     |
| Cough  |                        |                     |                        |
| subjects affected / exposed                      | 42 / 529 (7.94%)       | 0 / 30 (0.00%)      | 13 / 205 (6.34%)       |
| occurrences (all)                                | 43                     | 0                   | 13                     |
| Psychiatric disorders                            |                        |                     |                        |
| Insomnia   |                        |                     |                        |
| subjects affected / exposed                      | 28 / 529 (5.29%)       | 2 / 30 (6.67%)      | 9 / 205 (4.39%)        |
| occurrences (all)                                | 28                     | 2                   | 10                     |
| Investigations                                   |                        |                     |                        |
| Weight decreased                                 |                        |                     |                        |
| subjects affected / exposed                      | 58 / 529 (10.96%)      | 1 / 30 (3.33%)      | 20 / 205 (9.76%)       |
| occurrences (all)                                | 58                     | 1                   | 22                     |
| Blood creatinine increased                       |                        |                     |                        |
| subjects affected / exposed                      | 30 / 529 (5.67%)       | 3 / 30 (10.00%)     | 4 / 205 (1.95%)        |
| occurrences (all)                                | 34                     | 3                   | 4                      |
| Blood alkaline phosphatase increased             |                        |                     |                        |
| subjects affected / exposed                      | 20 / 529 (3.78%)       | 2 / 30 (6.67%)      | 2 / 205 (0.98%)        |
| occurrences (all)                                | 23                     | 3                   | 2                      |
| Injury, poisoning and procedural complications   |                        |                     |                        |
| Fall   |                        |                     |                        |
| subjects affected / exposed                      | 38 / 529 (7.18%)       | 0 / 30 (0.00%)      | 12 / 205 (5.85%)       |
| occurrences (all)                                | 51                     | 0                   | 14                     |
| Nervous system disorders                         |                        |                     |                        |
| Dizziness  |                        |                     |                        |
| subjects affected / exposed                      | 42 / 529 (7.94%)       | 1 / 30 (3.33%)      | 9 / 205 (4.39%)        |
| occurrences (all)                                | 46                     | 1                   | 10                     |
| Headache   |                        |                     |                        |

|  |                        |                     |                      |
|--|------------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 36 / 529 (6.81%)<br>40 | 2 / 30 (6.67%)<br>2 | 4 / 205 (1.95%)<br>4 |
| Blood and lymphatic system disorders             |                        |                     |                      |
| Anaemia  |                        |                     |                      |
| subjects affected / exposed                      | 161 / 529 (30.43%)     | 9 / 30 (30.00%)     | 26 / 205 (12.68%)    |
| occurrences (all)                                | 205                    | 10                  | 31                   |
| Thrombocytopenia                                 |                        |                     |                      |
| subjects affected / exposed                      | 91 / 529 (17.20%)      | 4 / 30 (13.33%)     | 9 / 205 (4.39%)      |
| occurrences (all)                                | 109                    | 6                   | 9                    |
| Neutropenia                                      |                        |                     |                      |
| subjects affected / exposed                      | 45 / 529 (8.51%)       | 0 / 30 (0.00%)      | 3 / 205 (1.46%)      |
| occurrences (all)                                | 68                     | 0                   | 4                    |
| Lymphopenia                                      |                        |                     |                      |
| subjects affected / exposed                      | 75 / 529 (14.18%)      | 5 / 30 (16.67%)     | 8 / 205 (3.90%)      |
| occurrences (all)                                | 102                    | 5                   | 10                   |
| Leukopenia                                       |                        |                     |                      |
| subjects affected / exposed                      | 66 / 529 (12.48%)      | 3 / 30 (10.00%)     | 4 / 205 (1.95%)      |
| occurrences (all)                                | 93                     | 4                   | 4                    |
| Gastrointestinal disorders                       |                        |                     |                      |
| Constipation                                     |                        |                     |                      |
| subjects affected / exposed                      | 103 / 529 (19.47%)     | 3 / 30 (10.00%)     | 23 / 205 (11.22%)    |
| occurrences (all)                                | 143                    | 3                   | 25                   |
| Abdominal pain                                   |                        |                     |                      |
| subjects affected / exposed                      | 30 / 529 (5.67%)       | 0 / 30 (0.00%)      | 6 / 205 (2.93%)      |
| occurrences (all)                                | 33                     | 0                   | 6                    |
| Vomiting   |                        |                     |                      |
| subjects affected / exposed                      | 97 / 529 (18.34%)      | 4 / 30 (13.33%)     | 12 / 205 (5.85%)     |
| occurrences (all)                                | 126                    | 4                   | 12                   |
| Toothache  |                        |                     |                      |
| subjects affected / exposed                      | 4 / 529 (0.76%)        | 2 / 30 (6.67%)      | 0 / 205 (0.00%)      |
| occurrences (all)                                | 4                      | 2                   | 0                    |
| Nausea   |                        |                     |                      |
| subjects affected / exposed                      | 187 / 529 (35.35%)     | 11 / 30 (36.67%)    | 33 / 205 (16.10%)    |
| occurrences (all)                                | 266                    | 11                  | 40                   |
| Flatulence                                       |                        |                     |                      |

|   |                           |                      |                         |
|---|---------------------------|----------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 529 (0.19%)<br>1      | 2 / 30 (6.67%)<br>2  | 1 / 205 (0.49%)<br>1    |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)   | 205 / 529 (38.75%)<br>231 | 5 / 30 (16.67%)<br>5 | 1 / 205 (0.49%)<br>2    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 101 / 529 (19.09%)<br>128 | 3 / 30 (10.00%)<br>3 | 5 / 205 (2.44%)<br>7    |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 4 / 529 (0.76%)<br>5      | 2 / 30 (6.67%)<br>2  | 0 / 205 (0.00%)<br>0    |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)                     | 37 / 529 (6.99%)<br>38    | 2 / 30 (6.67%)<br>2  | 8 / 205 (3.90%)<br>8    |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 8 / 529 (1.51%)<br>8      | 3 / 30 (10.00%)<br>4 | 4 / 205 (1.95%)<br>4    |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 117 / 529 (22.12%)<br>154 | 3 / 30 (10.00%)<br>4 | 26 / 205 (12.68%)<br>30 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 122 / 529 (23.06%)<br>141 | 4 / 30 (13.33%)<br>4 | 29 / 205 (14.15%)<br>29 |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 54 / 529 (10.21%)<br>60   | 3 / 30 (10.00%)<br>3 | 15 / 205 (7.32%)<br>16  |
| Osteonecrosis of jaw<br>subjects affected / exposed<br>occurrences (all)  | 7 / 529 (1.32%)<br>7      | 2 / 30 (6.67%)<br>2  | 1 / 205 (0.49%)<br>1    |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 45 / 529 (8.51%)<br>55    | 2 / 30 (6.67%)<br>2  | 12 / 205 (5.85%)<br>15  |
| Infections and infestations   |                           |                      |                         |

|                                    |                    |                |                   |
|------------------------------------|--------------------|----------------|-------------------|
| Cystitis                           |                    |                |                   |
| subjects affected / exposed        | 6 / 529 (1.13%)    | 2 / 30 (6.67%) | 0 / 205 (0.00%)   |
| occurrences (all)                  | 7                  | 2              | 0                 |
| Urinary tract infection            |                    |                |                   |
| subjects affected / exposed        | 54 / 529 (10.21%)  | 1 / 30 (3.33%) | 1 / 205 (0.49%)   |
| occurrences (all)                  | 71                 | 1              | 1                 |
| Metabolism and nutrition disorders |                    |                |                   |
| Hyperuricaemia                     |                    |                |                   |
| subjects affected / exposed        | 3 / 529 (0.57%)    | 2 / 30 (6.67%) | 1 / 205 (0.49%)   |
| occurrences (all)                  | 3                  | 2              | 1                 |
| Decreased appetite                 |                    |                |                   |
| subjects affected / exposed        | 112 / 529 (21.17%) | 2 / 30 (6.67%) | 30 / 205 (14.63%) |
| occurrences (all)                  | 132                | 2              | 32                |
| Hypocalcaemia                      |                    |                |                   |
| subjects affected / exposed        | 36 / 529 (6.81%)   | 1 / 30 (3.33%) | 7 / 205 (3.41%)   |
| occurrences (all)                  | 42                 | 1              | 10                |
| Hypophosphataemia                  |                    |                |                   |
| subjects affected / exposed        | 28 / 529 (5.29%)   | 0 / 30 (0.00%) | 7 / 205 (3.41%)   |
| occurrences (all)                  | 31                 | 0              | 9                 |
| Hypokalaemia                       |                    |                |                   |
| subjects affected / exposed        | 39 / 529 (7.37%)   | 0 / 30 (0.00%) | 7 / 205 (3.41%)   |
| occurrences (all)                  | 48                 | 0              | 8                 |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 16 January 2019 | Amendment 2.0: • Incorporated GB and DE only amendment changes. • Added statement of compliance as required by Sweden. • Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. • Clarified inclusion of and timing of start for best supportive/best standard of care. • Clarified inclusion/exclusion criteria. • Clarified procedures and timing. • Clarified progression of disease is not considered an AE or SAE. • Clarified start and end timing for 68Ga-PSMA-11 TEAEs, 177Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.  |
| 01 April 2019   | Amendment 3.0: • Updated sponsor name. • Updated background information data. • Clarified rPFS is an alternate primary endpoint. • Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility. • After Cycle 6, visits are now every 12 weeks (+/- 4 days). • Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up. • Plasma testosterone was added as an acceptable form of testosterone testing. • Window for QOL and Pain questionnaires added. • Updated reference section   |
| 08 July 2019    | Amendment 4.0: • Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients. • Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added. • Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%) and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023. • Additional imaging analyses details were added for study 68Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria. • Further clarification on the start and end timing for 68Ga-PSMA-11 TEAEs, 177Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs. • Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression. |
| 26 April 2021   | Amendment 5.0: • Extend Long-Term Follow-Up for up to an additional 12 months after V5.0 of the protocol is implemented at each site. • Reduce the procedures required for each Long-Term Follow-Up visit. • Add the requirement to report Serious Adverse Events related to the study drug during Long-Term Follow-Up as well as reporting details of renal toxicities and secondary malignancies. • Updated Serious Adverse Event reporting to reflect the change to Novartis Safety vs PrimeVigilance. • Update footers and headers so that all pages read V5.0. In V4.0 pages 73 to 95 still read "V3.0". No change was made to the content of these pages from V3.0 to V4.0; the error was typographical.  |
| 26 May 2022     | Amendment 6.0: • Extend the Long-Term Follow-Up for patients on this study to ensure consistent collection of long-term safety data until a new long-term safety follow-up study is available (to comply with FDA Postmarketing Requirement; estimated in 2Q2023).  |

|                   |   |
|-------------------|---|
| 14 September 2022 | <p>Amendment 7.0: The purpose of this protocol amendment V7 is to document the gap between the last visit of the patient under protocol amendment V5 and the first visit of the patient under protocol amendment V6 as there might be a time gap due to late finalization of protocol amendment V6.</p> <p>Details of the protocol amendments are as follows:</p> <ul style="list-style-type: none"> <li>· V5 extended the long-term follow-up by one year.</li> <li>· V6 extended further the long-term follow-up until a separate long-term follow-up study is available.</li> </ul> <p>Despite the time gap between these two protocol amendments V5 and V6, we suggest to continue the patient on the trial in order to comply with FDA post marketing requirements, so we continue to collect long-term safety data (with the same patient ID) for reconsented patient. An additional addendum of the informed consent is released with this protocol amendment V7 to document the patient's understanding to continue on study.</p> |
|-------------------|---|

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.  
Please use <https://www.novctrd.com/#/> for complete trial results.

Notes: